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PSYCHODYNAMICS AND THE ALLERGIC PATIENT

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IT has been known from ancient times that attacks of asthma could be precipitated by situations engendering anger and other emotional responses. Similarly, hay fever and certain dermatological conditions were recognized as being markedly affected by and perhaps even initiated by psychological forces. However, the influence of Virchow and Pasteur formulated a new morphological and mechanical era in medical thought.[4, 6, 13] This era was coupled with the rise of laboratory techniques of great precision, leading to a new immunology based upon physical and chemical principles. Incidental to this development of physicochemical influence, the role of emotional factors in the allergies was forced into the background to the extent that until the last few years none of the standard American books on allergy seriously considered these factors in a systematic way.

PRESENT RELATIONSHIP OF ALLERGY TO PSYCHOSOMATIC MEDICINE

Let us examine two medical journals, one devoted to psychosomatic medicine and the other devoted to allergy in the period from 1939 to 1946. During this period in the journal, *Psychosomatic Medicine,* there were published twenty papers relating specifically to emotional problems in the allergic state.[10] In the only American journal devoted to clinical allergy, published during the same period, there was only one brief report on the same topic. Surely this lack of communication between those interested in the solution of medical problems by psychosomatic techniques and those resting mainly on immunologic techniques is not desirable. In all fairness, not only have the allergists largely

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neglected certain important aspects of psychosomatic medicine, but the psychiatrists also, too often, are apt to neglect the massive structure of immunologic data which I have just touched upon. Why hasn't better rapport between the immunologic and psychologic techniques in medical practice been satisfactorily established?

THE A PRIORI FAILURE OF THE MODEL IN CLINICAL PRACTICE

For someone who has mainly published data on physicochemical mechanisms connected with immunologic processes in allergy to venture to give a paper on, "Psychodynamics and the Allergic Patient," might first be construed as a startling shift from a well-defined path of basic research. However, this is an assumption which frequently did not harmonize with my experience in the clinical practice of allergy during the last decade. This exploration of the utilization of psychodynamics in the practice of allergy is planned to determine through discussion what the allergist may expect in therapy from recent developments in the basic science of psychodynamics.[11] No matter how deeply our research in the fields of physics and chemistry takes us in attempts to provide models which explain the nature of immunologic and allergic processes, none of the models can ever *a priori* fully satisfy the physician in his daily therapeutic procedures, because none of these models ever completely reflects the complex pattern of the allergic individual.

The evolution of allergy as a clinical specialty depended upon progress and success in the correlation of anaphylactic data obtained from animals and man, with what was simultaneously discovered in the physics and chemistry of immunologic reactions.[3] New concepts, therefore, developed through proper observations of clinical manifestations of the tissue responses of man and animals, correlated with experiments like those of Obermayer and Pick, of Landsteiner[7] and his school, and of many others on the following:

1. The serologic specificity of proteins.
2. Cell antigens.
3. The nature and the specificity of antibodies.
4. The mechanism of sensitization by artificially conjugated antigens.
5. The mechanism of serologic reactions to simple chemical compounds.
6. Chemical investigation of nonprotein substances reacting specifically.
7. The mechanisms of antigen-antibody reactions in general.

In this attempt to relate chemistry and physics to immunology and to allergy, the experimenter, therefore, was, in the first place, always confronted with two questions: (1) What molecules are involved? (2) How do these molecules react as allergens to produce sensitizing antibodies which react specifically?

THE EXTENSION OF THE IMMUNOLOGIC MODEL TO A UNITARIAN THEORY: THE HISTAMINE THEORY AND ITS MANIFEST INADEQUACY

There was thus built up in the last half century a great field of physics and chemistry applied to immunology and allergy. These applications of the study of small and large molecules to clinical sensitization in man provided us with an extraordinarily useful technique in studying and treating the many clinical entities comprising the subject of allergy. The importance of this immunologic model for most of the clinical manifestations of allergy cannot be overestimated. Indeed, it has created the specialty of allergy. The drive for simplification by means of simple models led directly to a unitarian mechanism designed to account for all of the allergic patterns: The current histamine theory of allergy.* There is no doubt that histamine, which is a low molecular weight imidazole, does reproduce, to a certain extent, some of the manifestations connected with allergic reactions. Thus the wheal produced by histamine and the wheal produced by an allergen-antibody reaction are very similar. However, all skin reactions and even all wheals connected with the allergic state are not similar to those produced by histamine. Nor can the whealing responses to physical agents like light and cold be explained without eliminating the basic feature of the histamine theory: the rapid diffusibility of the histamine molecule. Indeed, I could use the entire space allotted to me describing how this histamine model, often used to explain conveniently almost every clinical and experimental entity of allergy, has been unjustifiably utilized.

What is the difficulty which prevents those who utilize physicochemical models from incorporating into their thinking and clinical utilization the rapidly growing science of psychodynamics? Is this desire to utilize models a characteristic of the growth of science in general, or is it something limited to the evolution of medical practice? I shall demonstrate that the use of models is a part of the development of science.

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*There have been many reviews purporting to show the importance of histamine in the production of clinical syndromes of allergy and in the production of anaphylaxis. However, all of these reviews, with few exceptions, are biased in favor of the theory, and evidence contrary to the theory is deliberately omitted. An exception is to be found in the excellent discussion made by Ratner in his book, *Allergy, Anaphylaxis and Immunotherapy* (Williams and Wilkins Co., 1943). In addition, the reader should consult Abramson, H. A.: "Present Status of Allergy," *The Nervous Child*, 7:86, 1948, where the evidence contrary to the histamine theory is also presented in an integrated form.

KELVINISM: FAILURE OF THE MODEL IN PHYSICS TO ACCOUNT FOR ALL PHYSICAL PHENOMENA

In 1932 the state of physics was in some ways analagous to the relationship of allergy with psychodynamics. The new experimental facts of relativity and quantum phenomena met with what can be termed an explanatory crisis.[2] Old ideas of mechanics and electrodynamics failed to explain the behavior of matter and of energy. The models which had been built up and had been utilized for many years were inadequate to account for the experimental facts of relativity and of radiation. Bridgman at that time pointed out that this crisis which confronted the physicist was only a repetition of what had occurred many times in the past. He mentions that similar crises confronted Prometheus when he discovered fire, and the first man who observed a straw sticking to a piece of rubbed amber or a suspended stone seeking the north star. Every kitten is confronted with such a crisis at the end of nine days. Whenever experience takes us into new or unfamiliar realms a new crisis of some type must develop. To quote Bridgman: "Now what are we to do in such a crisis? It seems to me that the only sensible course is to do exactly what the kitten does; namely, to wait until we have amassed so much experience of the new kind that it is perfectly familiar to us and then to resume the process of explanation with elements from our new experience included in our list of axioms." Even though physical models are the favorite of the physicists, the temporary and ultimately inadequate character of attempted physical explanations based upon models alone is brought out by the successes as well as the failures of Lord Kelvin to find a mechanical explanation for all physical phenomena. To quote from Lord Kelvin: "I never satisfy myself until I can make a mechanical model of a thing. If I can make a mechanical model, I can understand it. As long as I cannot make a mechanical model all the way through, I cannot understand it. But I want to understand light as well as I can, without introducing things that we understand even less of."

ANALOGY OF PROGRESS IN CLINICAL ALLERGY WITH PROGRESS IN PHYSICS

Just as the physicist was confronted with inexplicable facts about a score of years ago, so the allergist today frequently is confronted with phenomena not completely explained by the immunologic model which forms the basis of his specialty. In other words, one might say that in the study of certain cases classified as allergic, an explanatory crisis exists in the specialty of allergy similar to that which occurred in the much simpler science of physics in the 1930's. This situation in physics ultimately led

the physicist to incorporate into his thinking new theories having to do with relativity and radiation phenomena. New theories and new mechanisms do not ever clarify all of the unsolved problems. However, when the allergist consciously incorporates into his thinking the science of psychodynamics, even greater progress in the use of the immunologic model may be expected, because the incorporation of new ideas in science seems to stimulate further developments along classical lines. I shall shortly present some case records to illustrate how the immunologic or the classical model does not always completely account for the clinical syndromes in two groups of patients: (1) patients in whom allergy (immunologic basis) is present; (2) patients in whom the immunologic model cannot be demonstrated unequivocally in the light of present knowledge. Before presenting these case histories, let us define psychodynamics in more explicit terms.

PSYCHODYNAMICS AND PSYCHOMOTIVE FORCES

As you know, statics treats of the action of forces on bodies, the forces being arranged so that the bodies are at rest. The science which treats the action of forces on bodies in motion is called dynamics. It is convenient to say that the science which treats the action of psychological forces on behavior may properly be called the science of psychodynamics. The word behavior, as used here, includes the unit manifestations of the clinical syndromes of the allergies, such as the type of respiration, the response to skin stimuli, reactions of the patient to sensitizing antigens, or patterns analogous to those just indicated.

Rado[11] states, "Psychodynamics is the name for the theory which brings order into psychoanalytic observation and into the material of data ascertained by such observation. Psychodynamics represents the organized body of psychoanalytic findings, complemented by results obtained through other methods of research. Because of its singular value for the understanding of human behavior, psychodynamics must take its place in medicine as a basic science."

If possible, the foregoing definitions should be consciously incorporated into our clinical attitudes. The physiologist speaks of psychomotor reactions. Should we not, then, consider these psychodynamic factors as giving rise to psychomotive forces? I wonder if the term psychomotive force does not have some justification! There is an analogy with the term electromotive force. Electromotive forces may be engendered by various qualitatively different phenomena. Thus, if two dissimilar metals are placed in a dilute acid an electromotive force arises. Similarly, changes of free surface energy or changes in the physical state of the

surfaces, induced by the rubbing or the stretching of rubber, may give rise to electrical potentials. Can we not consider that various integrated neurobiochemical mechanisms, such as frustration, anxiety, guilt, hostility, et cetera, may give rise to psychomotive forces, the clinical effects of which will become more clearly delineated as the accumulating data are classified systematically?

It is recognized that Freud used the expressions motive force and motive power. However, a motive force is merely one which gives motion. It is not sufficiently specifically defined. It is necessary to designate the motive forces under discussion as those derived from the psyche, that is, specifically *psychomotive* forces. We must, therefore, also recognize the existence of *neuromotive* forces like those, to take a simple example, engendered by the antidromal impulses which produce a flare in the skin surrounding the histamine or allergic wheal.

With these definitions in mind, a fraction of my case histories, which proved to me that the conscious use of psychodynamics will be of value to the allergist, will be briefly touched upon.

CASE RECORDS ON PATIENTS IN WHOM THE DIAGNOSIS OF ALLERGY IS DEFINITE

Case 1.—C. was an unmarried man of forty years who was receiving perennial pollen therapy. Upon giving him his usual dose on one occasion and using the same extract, he got a very severe local reaction. I was unable to explain this reaction when he stated, "I am under unusually intense emotional strain at present. Do you think that this could have influenced the reaction? I believe so!" Whether emotional stress will increase the severity of local and general reactions to pollen allergens during treatment, I should like to leave to the Panel for discussion.

Case 2.—J. B., a theological student, stated, "When I have hay fever during September, something quite interesting occurs. I may have hay fever prior to preaching, but the hay fever disappears when I reach the pulpit."

Case 3.—A similar sequence occurred in an actress, K., who was sensitive to pollens and dust. K. stated that while she very frequently, during the season, had very severe hay fever in the wings of the stage, the hay fever disappeared when she faced the audience.

One may speculate in various ways on the mechanisms leading to the sudden diminution of the symptoms of hay fever in these apparently simple situations. It is, however, of still greater interest to take up in more detail the next case.

Case 4.—J. S., an unmarried man, twenty-five years old, was first seen in 1935. At that time he was extremely clinically sensitive to pollens and other inhalants. He also was skin sensitive to many foods. Trained as an engineer, he found it difficult at that time to obtain professional employment because of the business depression. He was extremely radical in his political views and did not take kindly to our form of government.

He responded poorly to specific therapy by injections of pollens and dust and by elimination diets. However, he himself developed a technique of controlling his asthma by a very interesting and surprising procedure. He stated, "When I feel an attack of asthma coming on, I get furious with myself for having the asthma, and this seems to avert the attack."

According to the results of certain studies on the psychogenic factors in asthma, it appears that the suppression of hostility may lead to intensification of asthma. In this patient there is evidence that some similar mechanism may have intensified his symptoms. The patient was advised to reconsider his hostile attitude toward our present social system and, if possible, to fit in with it. After several interviews he decided to become a government employe. He was sent to Albany, N. Y., by the government, where because of his skill he was rapidly promoted. He shortly thereafter made a satisfactory marriage, with a very definite change in attitude toward his whole life situation, modifying in addition his political views. His letters indicated that he was practically free of asthma but that he had mild residual hay fever which was readily controlled by pollen therapy.

Case 5.—Another instance in which repressed hostility led to a serious asthma attack was in Mrs. Q. From 1936 to 1940, when she was unmarried, she had received pollen and dust therapy with satisfactory results. However, subsequent to her marriage there occurred serious asthmatic attacks, which at first were ascribed to food sensitivity. On Friday nights she visited her mother-in-law. At these dinners the patient usually partook of fish in various forms. And since skin reactivity to fish was moderately positive, there did not seem to be much doubt that her asthma was induced by injudicious ingestion of what to her was an allergenic food. Unfortunately, the problem was not solved that simply. A serious asthmatic attack started one Saturday morning at 2:00 a. m. and persisted for four days unabated. The patient at that time was in her fourth month of pregnancy. After prolonged discussion, in which the patient's relationship with various members of the family who were present for dinner the preceding Friday evening was discussed, the patient became very upset and started to stammer in describing a conversation with her sister-in-law. It seems that her sister-in-law had remarked that the patient's abdomen was too large for a pregnancy in the fourth month. The violence of the attitude of the patient toward her sister-in-law, as well as the stammering, indicated that the relationship with the sister-in-law was strained. This expression of hostility to her sister-in-law coincided with the very rapid disappearance of her severe asthmatic condition. Except for the usual occasional mild wheezing spells readily controlled by inhalation of epinephrine hydrochloride, a quiet period of several months followed, during which her Friday evening asthma ceased.

This patient's skin reactions fit quite clearly and classically into the immunologic model. The patient had already been married for some time, and there was no reason to believe that premarital relations had caused the pregnancy. The hostility toward the sister-in-law and the violence of her response to the remark that her abdomen was large must be based upon other experience or fantasy. It was apparently these unknown experiences or fantasies, unknown both to the patient and the doctor, superimposed on the immunologic pattern, which led to the aggravation of asthma.

Case 6.—This patient, a married woman, thirty-two years old, had two children and appeared happily married. However, one year before she was

first seen by me, mild asthmatic attacks which had previously been easily controlled became so severe that the patient became incapacitated and could no longer take care of her family duties. She had had asthmatic attacks of a mild nature during the preceding ten years, particularly associated with upper respiratory infection. There was no history of seasonal hay fever nor clinical intolerance to other allergens. The patient had travelled a considerable distance to see me and arrived in New York City in a somewhat anxious state. In her first interview she revealed that during the preceding year no one had really been able to help her and that I was a last resort. At that time my attention was focused on experimental work with mists, which resulted in the stabilization of the particle size of the 1:100 solution of epinephrine hydrochloride. This new epinephrine mixture was prescribed. Much to my regret, the nebulizer and the solution which I had highly recommended were ineffective. I then advised her to take a teaspoonful of a mixture containing 5 grains of chloral hydrate three to four times a day and to discontinue the epinephrine injections and ephedrine capsules upon which she had previously depended. After this recommendation she came to see me the next day, sat down, pulled the bottle of chloral hydrate out of her bag, took a drink from the bottle and said, "You struck oil."

In spite of such optimism, the patient phoned several days later that her asthma was more severe than ever. I saw the patient within one hour of hospitalization. She received me sitting up in bed and breathing with difficulty. However, on examination of the chest, no râles were heard and the breath sounds were exaggerated. These findings were confirmed by a consultant. The patient's difficulty was evidently both respiratory and asthmatic.

After several hours, the patient developed a severe status asthmaticus. If there had been more delay in the chest examination, the respiratory difficulty without asthma would not have been observed. Subsequent conversation with the patient led to the disclosure that there was a very unhappy and difficult marital situation, details of which need not concern us at this time. In addition to the usual symptomatic therapy of her asthma, psychoanalysis was advised, and later was undertaken by the patient.

Case 7.—C., a twenty-four-year-old, serious minded, unmarried woman, lived with parents who had set up rather high standards for her. An ailing father, who was unable to work, made it necessary for her to continue working in order to contribute to the family support. Clinically sensitive to pollen, dust and a variety of foods, she was unequivocally classified as an allergic individual. At times she had difficulty in controlling her seasonal asthma as well as the asthma attacks which occurred between seasons. Very often she lost her usual response to ephedrine and epinephrine. For this reason it was necessary to explore at length, but nevertheless superficially, her life situation. This was not successful.

I finally decided that I would try to control her asthma by teaching her a form of breathing exercise, in itself a very definite type of psychotherapy. In it, the patient is instructed to extend the hands forward while inhaling; on exhalation the hands are brought to the side, but during expiration the expiratory breath is made very slowly and a humming, crying sound is made through the closed lips. It is very interesting to see the reaction of patients when the exercise is demonstrated. The crying sound, of course, has many implications, and nine patients out of ten smile in a queer and embarrassed sort of way. However, the patient took readily to this type of exercise and reported her ability to avert

attacks by doing the breathing exercises when she felt an attack coming on. Patients are advised to perform this exercise from one to two minutes every hour on the hour during a period of tension and difficulty in controlling the wheezing in the chest. This patient improved considerably on utilizing this breathing exercise. As a matter of fact, she was able to use this exercise in the subways when she felt heaviness in the chest, by thinking of the movements and of the crying expiratory whimper which she had been instructed to carry out.

One of the most interesting groups of allergic individuals that may be encountered is the group with bronchial asthma, with the respiratory pattern not typical of asthma. In typical asthma, as we know, there is difficulty in expiration. However, it is always wise to ascertain if there is not a superimposed difficulty in inspiration. When there is inspiratory as well as expiratory difficulty, I have found it practical not to rely entirely upon epinephrine, either by inhalation or by injection.

In cases where the inspiratory difficulty appears to be greater, sedation may be more important in controlling the attack.

In certain instances epinephrine may not work at all and these patients are often considered to be "adrenalin fast." However, these people are far from "adrenalin fast" in a pharmacologic sense for they may not have been taking epinephrine for months. An acute asthmatic paroxysm may occur which does not respond at all to epinephrine, irrespective of the amount given. I have one patient who received 6 cubic centimeters of epinephrine, 1:1,000 solution, subcutaneously, during the course of one night without relief, but who responded quickly to moderate sedation. Another case in point is one that I have observed recently.

Case 8.—This patient was a married woman of thirty years of age who had moderately severe asthma for one week which did not respond to epinephrine or ephedrine. She was hospitalized, and 3 grains of sodium amytal were administered after meals, three times a day, with 1.5 grains of seconal and 10 grains of chloral hydrate before retiring. In spite of this profound sedation, with a minimum amount of epinephrine given by inhalation, this patient was alert, active and became asthma-free. During this time, in spite of the high degree of sedation, she showed none of the ordinary sedative effects except the beneficial effect on her respiratory difficulty. As a matter of fact, this patient has periods free of asthma at home, followed by periods of severe asthma which is essentially uncontrolled by epinephrine but definitely controlled by sedation. Now this patient is really allergic, with positive skin tests, and she gets asthma when exposed to various inhalants including cat and horse danders. However, under exceptionally controlled conditions in which the allergic factors remained relatively constant, the severe degree of her asthma, I believe, depended to a great extent upon her emotional status. The complete data of this case illustrates a good example in which the superimposed psychodynamic factor must be controlled much more than the allergic component.

Case 9.—A schoolgirl of thirteen years of age had had periodic attacks of afebrile stuffed nose and sore throat. This began at the age of five when

she had begun coughing and had had frequent sore throats for which her tonsils and adenoids were removed. Since that time, she had had coughs and stuffed nose which were worse in September and October, suggesting ragweed sensitization. However, she also had had a stuffed nose very frequently in winter. At eleven, she became quite conscious of that fact. Her worse attacks, however, took place when the weather was consistently hot. This also fitted in with a diagnosis of constitutional hypersensitiveness. Her parents had paid considerable attention to keeping her in an allergen-free room with the usual precautions taken for mattress, pillow, rugs, curtains, et cetera. The patient had been told that she was constitutionally hypersensitive by her physician and had been given ragweed injections to no avail.

Physical examination of the patient was negative. There was a 7 per cent eosinophilia in the blood smear, confirming the diagnosis of allergy. There was no nasal discharge. Study of the skin reactivity revealed only suspicious reactions to a few foods. Reactions to ragweed pollen were slight with solutions containing 0.2 mg. N per c.c. Confirming the probability of ragweed sensitization was the presence of a moderate reaction to various tobacco extracts.

The clinical course of the patient, however, did not justify classifying this child as a simple case of hay fever. Late in May, during the grass season, she complained of a sore throat and clogged nose. On careful questioning, the sore throat turned out to be a lump in the throat, the patient herself stating that it was the "same that you get when you are about to cry." One week later, she visited her grandmother in a town nearby. As soon as she arrived at her grandmother's house, her nose became stuffed. This occurred fifteen minutes after she went inside the house, but cleared up while remaining within the house and was completely gone when she went to bed that evening. The following day, apparently helped by our discussion of the week before, instead of complaining to her mother of a sore throat, she told her mother that she had a lump in the throat. Her nose was not clogged and there was no cough. The lump in the throat this time lasted two or three hours and was relieved by steam inhalation. Again she explicitly stated to me that "my throat does not feel sore. Only feels as if something were caught there." After a few brief conversations the child was taught to distinguish between her emotional upsets on seeing her grandmother because she told her mother that "when I'm with Grandma I want no one there. Not even you—only Grandma." Further discussion led to the fact that she was anticipating the death of the grandmother. It was this idea which apparently had led to many of her symptoms.

She did not receive injections for her ragweed sensitization. Dust injections were given by her own physician. Her hay fever that year was so slight as to indicate that her pollen sensitization was a minor factor. The clinical course of the patient has been excellent without specific hyposensitization except for dust.

ALLERGIC PATTERNS IN INDIVIDUALS NOT PROVEN TO BE IMMUNOLOGICALLY ALLERGIC

In practically all of the cases with bilateral, wheezing respiratory difficulties (excluding tumors, stenoses, et cetera) which I have seen, there was some plausible type of immunologic, allergic or infectious basis. However, in the dermatoses, not in-

frequently there occur clinical entities similar to allergic responses where a true immunologic reaction cannot be unequivocally demonstrated. For example, a young married woman who was seen in 1940 complained of hives following ingestion of aspirin. Investigation revealed that she could take aspirin with no hives developing while under observation in my office, but on taking aspirin at home she invariably got hives. She had never had hives before her marriage. After her marriage she had almost always taken aspirin after quarreling with her husband. It ultimately became clear that it was not the aspirin but life situations of this type which led to hives.

In a study of several persons with hypersensitiveness (whealing response) to cold who were not immunologically allergic, a conflict situation was found in one case in an incident when the patient nearly drowned while swimming in the summer of 1941. A study revealed that these hives were apparently engendered by an unconscious death wish, the conscious realization of which led to a fairly rapid recovery. This case is of special interest and is given here in some detail.

Case 10.—A married woman, thirty-one years old, whose illness began on July 20, 1940, when she went swimming. On coming out of the water and drying herself as usual on the float in the sun, she discovered that she was "pink and itchy." This had never occurred before. She went into the water to cool off, but on coming out found that she was covered with small welts on the arms, legs and chest. Giant hives then formed all over the legs and arms, especially on the inside of the thighs. During the remainder of the time (eight weeks) which was spent near Long Island Sound, hives always formed on swimming if the immersion period was at all appreciable. The patient also noticed that on washing with cool or cold water, scattered hives also formed. This had never occurred prior to the first attack.

The patient had omitted the following fact in relating her history: she had almost drowned while in swimming the day before the onset, i.e., July 19, 1940.

Skin tests with a routine group of inhalants and foods were negative, and there was no history of food or other allergies, indicating that the patient belonged to the group having an allergic response without a true immunologic reaction.

There was no dermographia nor was there any electrical urticaria. To definitely classify the case as one of a whealing response to cold, the patient was tested with a standard cold stimulus. Well formed wheals, pseudopods, developed after as short a period as one minute of application of this standard stimulus. The maximum height of the wheal after one minute of application of the stimulus was approximately 1 mm. Much larger wheals with marked spreading without formation of pseudopods occurred after five minutes of application. The fact that cold had not previously caused whealing raised this question. Why had the onset of this response occurred at this particular time, that is, on a certain day after swimming?

During the summer of 1940, incidental to the war in Europe, she was

upset considerably. In the summer preceding the outbreak of the war, I saw the patient frequently. In 1939 she was gay and vivacious and more or less enjoyed life; in 1940 there was a definite tendency to be upset by war reports. Three friends for whom she had had a special esteem were actively engaged in the British and French navies, two in the submarine service and one on the French battleship, *Bretagne,* which had been sunk before the patient's present illness. Although the reports of the sinking of two submarines, each with one of her friends, occurred subsequent to the whealing response to cold, the death of one friend on the *Bretagne* at Oran occurred shortly before the abnormal response to cold was manifested.

The patient stated that she was a hypersensitive type because she fainted easily. She did not like the idea of skin tests. On further questioning she retracted the statement that she fainted easily and said that she did not really faint easily but "a sudden shock will cause prolonged periods of crying." She had, however, fainted before the onset of the present illness. The patient herself emphasized that anything sudden might produce an emotional upset: "If someone is suddenly rude to me, I am finished. If I tumble down the stairs, I might not be hurt but would cry."

After discussing the onset of the symptoms, the patient stated that a good many incidents relative to the development of the syndrome described did not become clarified until after a particular interview six weeks later. One evening thereafter, she *volunteered* the following information. She stated that while swimming toward shore on July 19, previous to the occurrence of the hives (the day when she nearly drowned), she had really felt that she wanted to drown. She stated that she felt that she didn't deserve to live while her friends serving in the armed forces, younger than she, possibly more useful to humanity than she, had to die while she remained alive. She was quite certain that this conflict existed during the two times that she "went down."

The striking feature is the suddenness of the onset following a period of mental conflict which endangered the patient's life. Since an immunologic mechanism always involves the presence of a complete or partial antigen, and since there is no type of conventional allergic sensitization discovered in the case in question other than what one could call the presence of a sensitized state psychologically, it is not apparent how one may think of the whealing response to cold described here as similar to the ordinary allergies. Rather, one must look here for a psychological pattern which can change the physiological processes in the system, as in this case, suddenly, in such a way that there is both a qualitative and quantitative change in the response of the minute vessels of the skin to the stimulus of cold. Although it may be argued that some immunologic reactions of the patient might have been altered, it is not likely that any known immunologic mechanism is primarily involved in the whealing response to cold itself in this case.

On one occasion when the patient had remained in the water about ten minutes, there occurred a severe skin reaction. In spite of the severity of this reaction, only slight dizziness was experienced. The main symptom was generalized itchiness, without anxiety, fainting feeling, or feeling of impending collapse. In other words, there was no general histamine-like reaction.

The patient moved to a cold climate after the acknowledgment of the conflict. She wrote (January 30, 1941), "Apparently you are quite right about my allergy—for the calmer I become about my friend's death the

slighter the trouble. I can put hand or foot in cold water now with no swelling, but if I go out in a cold wind, I return looking as though I had been having a bout with Joe Louis. However, it returns more or less to normal within an hour."

About one year after the onset of her illness, she returned for examination and reported the following details about the loss of her whealing response to cold. She stated that at first she was not convinced that the origin of her urticaria was psychological. However, she developed "a new point of view," made new friends, and gained 10 pounds in weight. Thereafter, she noticed that she did not wheal as usual. In the summer of 1941 the patient was taken to the same spot in which the conflict discussed in the foregoing was described. She swam to the same boat and back to the same pier. There was no evidence of any urticarial response whatsoever.

Case 11.—In the following case, the allergen was accidentally suggested to the patient. B. was a pretty girl of nineteen, well dressed for a clinic patient, with better manners than usual and better education than one ordinarily encounters in the clinic in question. She complained of hives of six months' duration. This patient's skin tests were negative. However, elimination diets were of no avail. About ten days before Christmas in 1941, various allergic possibilities causing hives were discussed with the patient. The role of inhalants was mentioned, and I accidentally said that perhaps even the odor of Christmas trees which were then being offered for sale could produce hives in certain individuals. The patient apparently seized upon the suggestion that the odor of Christmas trees was causing her hives. The following week, she came back full of confidence, for she was able to produce hives on going close to a large number of Christmas trees then being sold. During the following month (January, 1942) the hives persisted even though she was no longer exposed to Christmas trees. This was pointed out to her. She was asked if she could make sense out of the whole thing. She then requested to speak to me privately. We went to another room where no one could overhear our conversation. She wept bitterly. Her parents had separated when she was quite young. The burden of her education and upbringing fell upon her mother. She felt that she was not receiving all of the education and its advantages which she desired and required. The patient was placed on a full diet. In a period of months her attacks of hives were replaced by milder and less frequent episodes.

It may be argued in this case that our immunologic model in my hands did not serve satisfactorily. Be that as it may, it was quite evident from the course of the case that the suggestion that the odor of Christmas trees produced hives was followed by the production of hives. This case is presented to show that a pattern classically allergic may also be produced by conditions in which the immunologic model as yet is not clear cut, if, indeed, it is present at all.

Case 12.—An unmarried lawyer, A. B., thirty-eight years old, complained of asthma, eczema and hay fever. His symptoms had been present periodically for about six months.

Each one of these complaints merits separate attention. At no time while the patient was under observation was any asthma noted, nor could he justify his history of asthma by a description of a true asthmatic attack. There was present some difficulty in breathing or some modification

of the respiratory cycle at times. This respiratory difficulty was misinterpreted by the patient and his friends.

The eczema was localized to the scalp and was diagnosed as mild seborrheic dermatitis which readily responded to appropriate treatment.

The complaint of hay fever seemed to be justified and was essentially the main symptom. It was not induced by temperature changes, nor was it exaggerated by dust, perfumes, foods or any of the allergens responsible for rhinitis. The family and past personal history for allergy was negative.

The patient was well developed, well nourished, co-operative, far above the average intelligence, and a meticulous person in dress and in manners. Rapport was readily established when the usual medical matters were discussed. It was evident, however, that the usual routine physical and laboratory examinations were not only important from the point of view of the physician but also from that of the patient, who showed more than a casual interest in their outcome. Physical examination, as well as laboratory findings, were negative, including the skin reactivity to an extensive series of allergens, including dusts from various sources, pollens, foods and mold spores. There was no local condition in the nose to account for the symptoms nor was there any eosinophilia in the blood.

A more detailed analysis of the time of occurrence of the hay fever was undertaken. The patient finally revealed that his hay fever occurred chiefly after fatigue or nervous strain. He volunteered that if he stayed up late at night he had severe hay fever the next day. In spite of the fact that the patient recognized the relationship of these nasal symptoms to his emotional state, this recognition did not result in any diminution of symptoms. The patient challenged me to do something about his symptoms. The usual local medicinal therapy was employed to no avail. On a basis of empiricism, injections of dust and stock "cold" vaccine were suggested but were rejected by the patient.

The patient was discharged without relief and went to another city. Four months later, the patient reappeared and announced that his hay fever had practically disappeared but that he was feeling very depressed and was extremely unhappy. After some discussion he made the following disclosure: During the time that the allergic status of the patient had been investigated, he had been interested in a young woman whom he had seriously considered marrying. During his absence she had married someone else. It was this fact which occasioned his feeling of depression, coincident, however, with the disappearance of his "hay fever." He emphasized that he had really always been very uncertain in his attitude toward the young woman in question. He was extremely perturbed because he felt that he had not done the right thing by not marrying her. During subsequent conversations which touched on personal relationships and obligations, he appeared to be much relieved and much more cheerful. He then made a special appointment when he appeared with a new friend, feminine, blonde, and attractive, and without much ado he introduced the young woman and then said goodbye.

Case 13.—The effect of a suppressed conflict on the origin of "allergy" to light has to my knowledge not been shown hitherto.[1] A patient who responds to irradiation by ultraviolet light by whealing of the skin has been studied, both from a physiological and psychological point of view. Although these studies are not complete, it is desirable to report progress made thus far. The patient is a married woman, W.G.H., forty years of age, whose skin shows a general response of hypersensitiveness to ultra-

violet light by a whealing reaction over all the body surfaces studied. The wave length at which whealing may be produced begins very close to 3,700 Å and extends to lower wave lengths with increasing sensitiveness in the region where absorption by the outer epidermis occurs. The patient

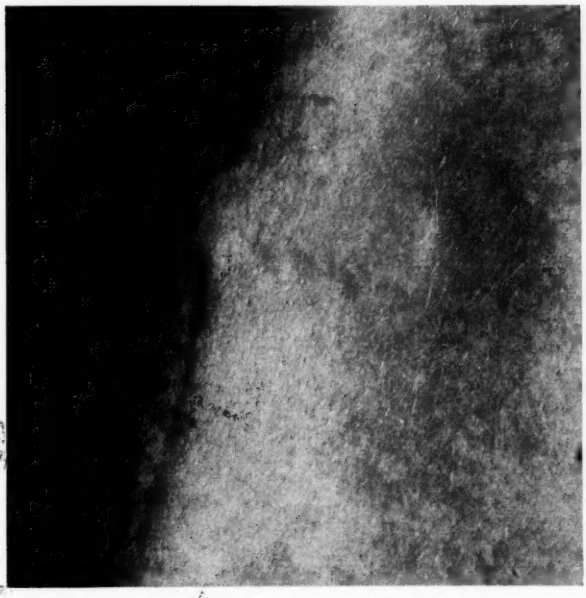

Fig. 1. Compare the sharp edge of the typical whealing response to light with the irregular edge of the wheal produced by histamine (electrophoresis). This is evidence that the light reaction is not caused by a small molecule like histamine.

was referred by another physician who had explored therapy from the point of view of many of the theories dealing with the whealing response, including a high calcium diet, vitamins, as well as irradiation of the blood serum itself, followed by re-injections. The patient was subjected to many types of conventional therapy without any success. The *original* history of the patient was as follows:

Approximately eight years before the patient came under observation, she went swimming at a nearby beach. She remained on the beach several hours. Following this exposure to sunshine on the beach, she suffered an attack of "sun stroke" and remained in bed, ill, for two weeks. When she recovered from her attack of "sun stroke," she noticed that she swelled up whenever she went out into the sunshine, especially in the summer sunshine. She could expose herself to sunshine in the winter to a certain extent. Protection by window glass was incomplete. The severity of her skin reaction was so great that she was unable to perform her ordinary duties as a housewife. In the summer, it was almost impossible for her to go out into the street because, even though she carried a parasol, reflected ultraviolet rays caused very severe edema of the ankles and legs.

Similarly, even when driving in a motor car, the reaction to reflected ultraviolet was quite severe unless the windows were closed.

After being under observation and submitting to many tests for a period of three years, a state of anxiety supervened. She related her symptoms

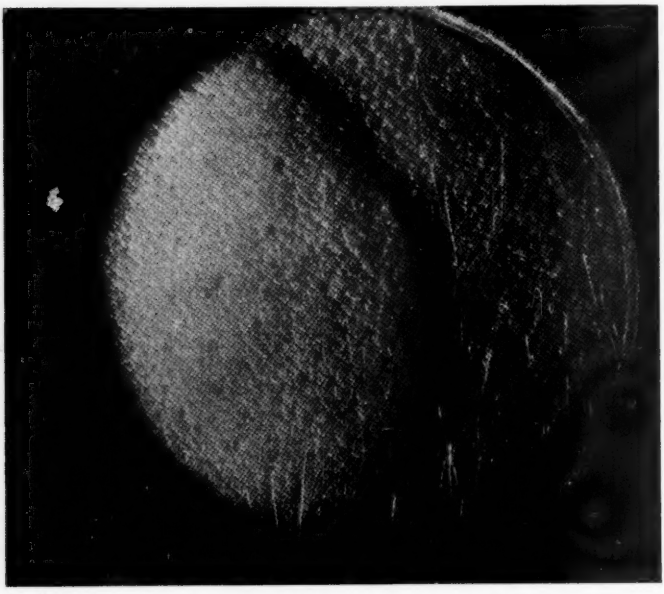

Fig. 2. Whealing response to cold produced by a standard stimulus. Note the absence of pseudopods. Magnification X 3.

to "early change of life," and endocrine therapy was instituted. At the same time, her history was cautiously re-explored, especially concerning the exact time when the whealing response to light first occurred. After many interviews, the following additional aspects in the history became clearer.

The patient and her sister were orphans and had lived together as unmarried girls. Subsequent to the marriage of the sister, the patient resided with her sister and husband. During the time that she lived with her sister, the sister's husband made advances which were rejected by the patient. Because of this difficult situation, she was forced to leave her sister's household without an adequate explanation. This gave rise to a complex family situation.

On careful questioning, it appeared that on the day the patient was in swimming (the day subsequent to which she developed *urticaria solare)* the sister and her husband unexpectedly appeared at the beach. On seeing her sister and her brother-in-law, the patient ran into the water and remained partially submerged in the water for three hours, explaining to me: "I did not want him to see me in my bathing suit." It was only after her sister and brother-in-law had left the beach, that she came out of the water and subsequently became ill.

After tracing the events of the intervening years, during which she had married and there had been no amelioration of the difficult family situation, the patient's present and newly precipitated state of acute anxiety seemed to have been occasioned by an unexpected visit of her brother-in-law when she was at home alone. This unexpected visit had preceded her new symptoms.

Further questioning only led to a repetition of the above story. The seriousness of the emotional reaction of the patient led to further exploration. It appeared that something in our folklore would lead to an explanation. It was customary in Biblical times for a husband, on the death of his wife, to marry the sister of the wife. This was cautiously explained to the patient and she was asked if any situation corresponding to that ever arose. Her answer was immediate. She said, "Of course. He always told me, 'When your sister dies, I'm going to marry you.'" No attempt has been made as yet to explore this lead, although the conflict situation produced anxieties and organ neuroses readily "cured" by placebos. Her sensitivity to light has persisted unchanged.

The most common cause of the skin wheal, dermographism has no immunologic basis whatsoever.

EMOTIONAL DISTURBANCES—CAUSE OR EFFECT?

The relationship of the emotional disturbance to the development of the allergic pattern may be considered from two points of view. In the first place, the emotional disturbance may play a role in choosing the organ and changing the neurovascular system so that the thresholds are lowered and the intensity of the allergic pattern is increased or decreased. In the second place, the resultant allergic syndrome may have a special effect itself on the emotions of the individual so that a vicious cycle arises. This question has been considered by Rogerson, Hardcastle and Duguid,[12] who asked whether the intense need of children with bronchial asthma for mother's love is one of the causes of their asthmatic condition or a result of it. There was much to suggest that the acute dependence on the love of the mother might result from the asthmatic attacks themselves. If I may quote French:[5] "A severe attack of asthma, with its acute threat of suffocation, is a terrifying experience and one in which the patient feels completely helpless. What wonder, then, that a child who is constantly threatened with the danger of suffocation and whose activity must be limited for fear of bringing on an attack should feel the need always to have near him a mother to whom he can cling? There is, accordingly, every reason to expect that the asthma attacks themselves should induce just the sort of helpless dependence that has been found to be characteristic of the deeper emotional life of our asthma patients. May not the personality traits that we have been describing be merely a secondary reaction to the disease itself?"

There are, of course, too few data to draw any unequivocal conclusions. I hope that the members of the Panel and of the College will discuss, for the record, in what way they believe

that the allergic patterns, especially asthma and skin manifestations in the infant, in the child and during later life, may influence the personality structure.

THE COMBAT EQUIVALENT IN THE ALLERGIC PATIENT

It was shown by Peshkin[8,9] in 1922 that in a group of 500 children considered otherwise relatively normal (no clinical allergy), approximately 10 per cent showed positive skin tests to a variety of allergens. He observed these children during a period of years. He found that some of these immunologically positive children were often precipitated into acute episodes of clinical allergy, especially asthma, by other presumably unrelated conditions, as for example, whooping cough, measles, pneumonia, upper respiratory infections, and even following operations for the removal of tonsils and adenoids. It is of interest that Peshkin regarded these superimposed diseases or procedures as the initiating factors which led to the clinical manifestations which had been viewed in a preliminary way by the immunologic reactions in the skin. In 1926, Peshkin further developed his concepts to the point where he proposed the clinical syndrome of para-asthma. The term para-asthma was introduced to segregate bronchial asthma due to immunologic hypersensitiveness from asthma not due to immunologic hypersensitiveness. Similarly the term para-allergy may be utilized. Since infection or trauma could influence the onset of allergic patterns in individuals previously shown to be allergic without clinical patterns, why cannot disturbances neurogenic in essence produce similar reactions, perhaps even to initiate them? These could be included in the para-allergy group. All of this implies that the immunologically allergic individual already has patterns carved as it were by his response to allergens. In the individual without known immunologic patterns, these patterns nevertheless exist, as we know from clinical experience. These patterns exist just below an explosive threshold where another stimulus, such as a difficult life situation, may result in an overwhelming clinical response. These life situations can possibly be considered analogous to combat equivalents. The argument may be raised that combat situations are not similar to ordinary life situations. That view is open to question. The combat situation really occurred the first day war was declared or war was imminent. It might have expressed itself clinically upon notification by the draft board to report or in more rugged individuals only after prolonged periods of combat. If one accepts the point of view that many of these individuals who have been subjected to difficult combat situations were subsequently successfully treated by physicians rapidly trained in psychodynamics, we might have another basis for rapprochement between allergy and psycho-

dynamics. This possibility will be touched upon briefly in the next section. In it we will assume that the allergic individual faces, in his daily routine, life situations which may be combat equivalents. The immunologic model and the clinical pattern has already been deeply carved into his physiologic structure so that given certain types of life situations the clinical response is very much out of proportion to the situation itself.

FUTURE PROGRESS

There are two steps necessary to achieve a fundamental advance in the specialty of allergy as far as its relationship to psychodynamics is concerned. The first step involves a change in the editorial policy of the leading journals devoted to allergy and to psychosomatic medicine itself. It would, for example, be refreshing to find case records in the journal, *Psychosomatic Medicine,* showing that a pattern typically psychogenic in nature turned out to be based upon an immunologic mechanism. Similarly, contributions designed to emphasize the role of emotional factors in the allergic patient must be encouraged, even sought, by the editorial staffs of the allergy journals.

The second step involves systematic postgraduate instruction in psychodynamics. Ideally, a personal psychoanalysis should be a requirement for the study of psychodynamics. But at present this preparation must, in general, be reserved for the student and the younger physician. Few of this younger group will become psychoanalytically trained allergists under our present system of training and specialization. Cannot this problem be answered by comparable situations of the last war? The acute war neuroses were often successfully treated by physicians rapidly trained in psychodynamics. If the great mass of data which now comprises the basic science of psychodynamics were to be classified into a form capable of being more easily understood and applied by the allergist, an important advance in the science and practice of allergy itself would take place. Allergy would then become a more useful specialty than that which could be provided by either the allergist or by the psychiatrist working alone.

Some may conclude, in view of our present knowledge and attitudes that these steps are either undesirable or impossible to attain. However, an appreciable number of my colleagues and I believe that with proper instruction and proper sympathy, this program is neither impossible nor undesirable. The success of this proposed publication and instructional program cannot be estimated until a serious attempt is made to carry it out under suitable auspices. Without such an attempt, neither group will be able to understand the other or help the other group to synthe-

size the complicated psychosomatic syndromes under discussion, during our time. With this attempt, perhaps implemented and encouraged by this Round Table, a new and broader phase of clinical allergy will have been initiated.

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SKIN TESTS WITH ENDOCRINE SUBSTANCES

Method of Zondek and Bromberg

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IN 1934, Sulzberger, Rostenberg and Sher[10] reported on skin tests with hormones in cutaneous diseases, notably acne vulgaris, and in the text book on *Dermatologic Allergy* Sulzberger[9] reviewed the experimental data on endocrine allergy and discussed at length the possibility that acne and other dermatoses might be related to the allergic hypersensitivity of cutaneous structures to autochthonous hormones. In addition, among others, Simon[7,8] and Loveless[8] have reported experiments demonstrating the existence of true allergy to hormones.

More recent and extensive studies were reported in 1945 by Zondek and Bromberg,[12,13] who obtained positive skin tests with a large variety of hormones and interpreted their results as indicating a state of allergic hypersensitivity to hormones produced by the endocrine glands of certain individuals. Among the various diseases in which they found some cases to be due to hypersensitivity to hormones, there were several of dermatologic interest. The present study, which was restricted to tests with steroid hormones, was undertaken to examine the diagnostic and therapeutic applicability of the method of Zondek and Bromberg in a larger dermatologic material.

Zondek and Bromberg observed the existence of a state of hypersensitivity both to protein-like hormones, e.g., insulin and pituitary secretions, and to steroid hormones (estradiol, progesterone, testosterone, and corticosterone). Hypersensitivity to the steroid hormones, or to the products of their metabolism which are excreted in the urine (estrone, pregnandiol, and androsterone), was demonstrated by cutaneous tests with oily solutions; such tests usually became positive within twenty-four to forty-eight hours. Hypersensitivity to insulin and chorionic gonadotropin was demonstrated by cutaneous tests with aqueous solutions; such tests usually became positive after a shorter reaction time.

The conditions included in their study[9] were cases of the following diseases in which certain pathological conditions became manifest in relation to menstruation or menopause: (1) asthma, (2) vasomotor rhinitis, (3) angioneurotic edema, (4) chronic urticaria, (5) chronic eczema, (6)

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From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology of the New York Postgraduate Medical School and Hospital (Director: Dr. Marion B. Sulzberger).

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acne, (7) migraine, (8) superficial keratitis, (9) premenstrual tension, (10) pruritus vulvae, and (11) premenstrual fever.

The following items are listed by Zondek and Bromberg[12,13] as evidences of endocrine allergy:

1. Positive skin tests demonstrating hypersensitivity to oily solutions of steroid hormones or to their products of metabolism.

2. The "recurrent test reaction," i.e., specific flare-up of the original cutaneous test site when a larger quantity of the same steroid hormone is injected subcutaneously twenty-four hours later at a second site. This reaction tends to show that the reaction to the particular hormone is specific.

3. The "retarded or periodic retarded reaction," i.e., the premenstrual flare-up of a specific test site occurring in the same phase of one or more successive menstrual cycles indicating sensitivity coincident with the peak concentration of the hormones in the body.

4. Serious reactions of an allergic nature following the injection of even minute amounts of steroid hormones in allergic patients not previously treated with hormones.

5. The ability to demonstrate the presence of specific reagins to a hormone by means of passive transfer tests.

6. The "endogenous passive transfer test," i.e., when during the premenstrual phase "normal" subjects were injected intracutaneously with serum from patients hypersensitive to estrone or estradiol, they gave positive cutaneous tests. This demonstrates that serum reagins can produce positive cutaneous reactions when the allergenic hormone reaches its peak value in the body of the "normal" patient.

7. Similarities in the properties of hormone reagins and ordinary reagins.

8. The fact that patients with a positive cutaneous reaction to a hormone often give a personal and family history of allergic disease.

9. The fact that hyposensitization with the allergenic hormone is often accomplished with satisfactory clinical results.

PREPARATION OF THE STEROID HORMONE TEST SOLUTIONS

As previously stated, we restricted ourselves to tests with steroid hormones. This was done because of the infrequent occurrence of positive reactions to pregnandiol, insulin and chorionic gonadotropin, as reported by Zondek and Bromberg. The materials used by us included the recrystallized steroid hormones estrone, estradiol, progesterone, testosterone, androsterone and desoxycorticosterone acetate; in addition to these, cholesterol and the olive oil vehicle alone were used as control materials.

The steroid hormones and cholesterol were dissolved in neutralized olive

oil.* This was accomplished by heating each of the mixtures at 100° centigrade for twenty-four hours, until a sterile, clear, and homogeneous solution was obtained. All substances were prepared in concentrations of 1 mg. of hormone in 1 c.c. of olive oil, and were dispensed in sterile rubber-capped vials.

METHODS OF TESTING

In the beginning we used the volar surface of both forearms, and all tests were made by the classical intradermal technique, as suggested in the original paper by Zondek and Bromberg.[12]

Fifty-six subjects were tested by this method. The almost regular appearance of local reactions which were equal to or greater than the positive reactions described by Zondek and Bromberg led us to question the correctness of our method of testing. It was evident that 0.1 c.c. of the olive oil vehicle, with or without the steroid hormones, when injected intradermally, acted to produce local nonspecific reactions.

Subsequently, in a personal demonstration by Dr. Zondek, we were shown that the method which he and Bromberg had actually used[13] was to insert the needle through the epidermis to a level *somewhat deeper* than that usually used for intradermal testing. When the oily material was injected in this manner, a small elevation of the skin was produced which disappeared almost immediately. The injections were made into the lateral aspects of the arms and the radial aspect of the forearms as follows: in the right arm, the proximal site with cholesterol and the distal site with estradiol; in the right forearm, the proximal site with estrone and the distal site with progesterone; in the left arm the proximal site with the olive oil vehicle and the distal site with testosterone; and in the left forearm, the proximal site with androsterone and the distal site with desoxycorticosterone acetate. In order to be able to exactly locate the site of injection by this method at the time of reading each site was indicated by a skin marking pencil.

READING OF THE CUTANEOUS TESTS

The tested areas were observed twenty-four and forty-eight hours after injection. A reaction was considered positive (Table I) when, twenty-

*Neutralized olive oil was prepared exactly as did Zondek and Bromberg, i.e., according to the Helvetia *Pharmacopoeia VI*, as follows:

Olive oil	500.00 grams
Sodium carbonate dekahydrate Rgt. q. s.	
Distilled water q. s.	
Sodium sulfate anhydrous	25.00 grams
Sodium chloride C. P.	12.50 grams

The acid value of the olive oil is first determined. This value multiplied by 0.6 gives the necessary quantity of crystalline sodium carbonate for 100 parts of oil. The sodium carbonate is dissolved in one half its weight of distilled water at 40° C. and added to the oil which has also been warmed to 40° C. Shake frequently and vigorously for 24 hours. The acid value is determined and if not sufficiently low, shaking must be continued until the correct value is reached. Then 5 parts of sodium sulfate anhydrous and 2.5 parts of sodium chloride are added to the oil and the flask is vigorously shaken. After 12 hours the mixture is filtered and the filtrate put into 100 c.c. flasks. These are stoppered and sterilized by heating at 115° C. for 15 minutes in an autoclave. Protect from light.

Assay.—Must meet the specifications of the olive oil monograph; however, the acidity must not be higher than 0.2 which corresponds to a maximum content of 0.0565 per cent of oleic acid in neutralized sterilized olive oil.

four or forty-eight hours after injection, a red or rose-colored slightly elevated area, at least 1.5 cm. to 3.0 cm. in diameter, appeared at the site of injection. Even when the twenty-four-hour reading was negative or inconclusive, a second reading was made at forty-eight hours.

TABLE I. EVALUATION OF REACTION TO CUTANEOUS INJECTIONS OF STEROID HORMONES

Reaction After		Evaluation
24 Hours	48 Hours	
+	+	Positive
−	+	Positive
+	−	Positive
−	−	Negative

The "recurrent test reaction" was used in those instances when doubtful reactions were observed in the regular test, e.g., in cases of positive reactions which appeared three to five hours after injection and disappeared a few hours later, or in cases of doubtful positive reactions at twenty-four to forty-eight hours. The routine of the "recurrent test reaction" is as follows: twenty-four hours after the cutaneous injection of 0.1 c.c. (0.1 mg.) of the test hormone, 1.0 c.c. (1.0 mg.) of the particular hormone which produced a doubtful reaction is injected *subcutaneously* at a site removed from the original test area. The test is considered positive if, three to five hours after the second (1.0 c.c.) injection, the original cutaneous test site evidences reddening accompanied by itching.

Our subjects were also observed for the "retarded reaction" and "periodic retarded reaction." For example, reactions which were negative at the twenty-four and forty-eight-hour readings but became positive just prior to the succeeding menstrual period were considered "retarded reactions"; and positive reactions which recurred spontaneously at the same test site during the premenstrual period of several successive cycles were considered "periodic retarded reactions."

We did not perform any passive transfer tests during this study.

SUBJECTS

The patients used for these tests were taken from among those at the clinic and in private practice.

A total of 102 patients was tested. There were sixteen men and eighty-six women. Thirty-eight of the eighty-six women presented dermatoses occurring with or apparently aggravated by menstruation or menopause. The remaining forty-eight women in whom the dermatosis presented no apparent relationship to endocrine function, together with the sixteen men, served as controls. As the work was done in the allergy department of the New York Skin and Cancer Unit, many of the "control" subjects presented eczematous, eczematoid and urticarial eruptions, including a substantial number of cases of a probable allergic etiology.

TABLE II. PATIENTS WITH DERMATOSES APPARENTLY RELATED TO MENSTRUATION OR MENOPAUSE

Dermatosis	Number of Cases Tested	Number of Hormone Sensitive Cases	Hormonal Allergen	Effects of Hyposensitization Therapy	Number of Cases With Questionable Reactions of Any Type
Acne	12	1	Progesterone	Not done	2
Urticaria	7	2	Estradiol	Satisfactory	3
			Estrone	Satisfactory	
Pruritus vulvae	4				1
Eczema	3				1
Pruritus ani	1	1	Estradiol	Not done	
Generalized pruritus	1				1
Acne rosacea	1				1
Keratoderma climactericum	1				1
Keratosis follicularis	1				1
Recurrent aphthous ulcers	1				
Seborrheic dermatitis	1				

RESULTS

Subjects with Dermatoses Apparently Related to Endocrine Function

Of the thirty-eight patients tested, having dermatoses apparently related to endocrine function, our skin tests indicated that five were apparently hypersensitive to the olive oil vehicle and therefore were excluded from further study. Of the remaining thirty-three patients, four presented their dermatosis as chronologically related to menopause, and twenty-nine as related to menstruation. The dermatoses studied (Table II) were as follows: acne twelve, urticaria seven, pruritus vulvae four, eczema three, pruritus ani one, generalized pruritus one, acne rosacea one, keratoderma climactericum one, keratosis follicularis one, recurrent aphthous ulcers one, and seborrheic dermatitis one.

Four of these patients gave what were considered as positive reactions to the hormonal tests. Three of these gave positive reactions at the time of regular readings of the tests; one case of urticaria was positive to estrone; one case of urticaria was positive to estradiol; and one case of acne was positive to progesterone. The fourth patient, complaining of pruritus ani, was negative at the time of testing but gave a positive "retarded reaction" to estradiol prior to the succeeding menses.

Eleven patients gave questionable and inconclusive responses of various types. Six patients gave questionable reactions to one or more test substances at twenty-four hours alone or at both twenty-four and forty-eight hours. Four of these were tested a second time because of questionable reactions obtained with the first tests. The second tests did not give additional information. There were questionable "retarded reactions" in two patients. The "recurrent test" was done in three of the patients giving questionable reactions during the first tests, without obtaining a positive response in any case.

Unfortunately, two of the patients with positive reactions (the patients with acne and pruritus ani) could not be followed. The two patients with urticaria who gave positive reactions on cutaneous testing were hyposen-

sitized by repeated subcutaneous injections of ascending doses of the specific endocrine substance which had produced the positive skin test; both patients obtained marked relief from their disease.

Case 1.—A married woman, aged thirty-seven, mother of one child, complained of chronic urticaria with premenstrual exacerbations.†

The patient had recurrent attacks of urticaria since childhood, with rather severe attacks at the ages of ten and eighteen. In 1941, the patient noted that the attacks were becoming more severe and were occurring more frequently and that there was a marked flare-up of the urticaria during the premenstrual period. Therapy for a three-month period, consisting of stilbestrol and thyroid, produced some improvement of her condition.

During the next four years there were continued recurrent attacks of urticaria, for which numerous methods of treatment were tried, including calcium strontium bromide, ephedrine and Nembutal capsules, epinephrine, charcoal tablets, calcium gluconate, dilute hydrochloric acid, prostigmine drops, vitamin C, Hapamine, Benadryl, elimination diets and autohemotherapy; moderate temporary relief was affected by these methods. Hypnosis also was used and almost completely relieved the itching, but had no effect on the number or severity of the urticarial attacks.

In 1945, because of the definite premenstrual flares of the urticaria, which had been particularly troublesome for the eighteen months preceding, Dr. A. C. J. Simard instituted "autogenous" therapy with material prepared by Dr. Julius Pincus from the menstrual discharge of the patient, collected at the beginning of the flow; after dilution with saline and sterilization by Seitz filtration this was given in small subcutaneous doses every other day for a period of about five weeks. This treatment effected a complete subsidence of all urticaria.

The patient remained free of all urticaria until July, 1947, at which time a premenstrual flare-up of the urticaria was noted. Pyribenzamine aided in controlling the severity of the eruption. On August 12, 1947, the hormonal tests with endocrine substances were performed. At twenty-four hours the estrone site was positive (2 by 2 cm.) and at forty-eight hours the same site was still positive but the reaction was diminished in intensity. A "recurrent test" performed on August 14 was negative.

In view of (1) the history of premenstrual flare-ups of the patient's urticaria, (2) successful previous hyposensitization with autogenous menstrual discharge, and (3) a positive reaction to estrone on skin testing, hyposensitization with estrone was attempted. Daily subcutaneous injections of Theelin in oil (Parke, Davis), which is estrone in peanut oil, were given beginning with 0.1 c.c. In spite of maintaining the dose at 0.1 c.c. daily for a period of one week, the patient occasionally had exacerbations of her urticaria. It was impossible to ascertain whether or not the hormonal injections were the cause of these exacerbations. The dose was then gradually increased, and a total of thirty-two injections were given daily except Sundays. Thereafter, they were given three times weekly until a total of forty-three had been administered, the last five being 1.0 c.c. administered intramuscularly. Treatment was discontinued on October 24 because the patient complained of increased menstrual flow with an accompanying severe headache. Upon completion of therapy, the patient stated that she was "98 per cent" improved, with only an occasional urticarial lesion.

During the period of hyposensitization, the use of Pyribenzamine was not denied. Whereas the patient took up to 400 mg. a day at the beginning of treatment, the dose was decreased to none or 50 mg. a day at the end of treatment. It was interest-

†We are indebted to Dr. Charles R. Rein for referring this case.

ing to note that on several occasions the site of injection of the previous day flared when the succeeding injection was given ("recurrent test reaction?"). The flare-ups of the urticaria became progressively less toward the end of therapy.

The two subsequent menstrual periods (November 21 and December 18) were normal in character, with only a very slight increase in the number of urticarial lesions premenstrually.

On January 12, 1948, we retested the patient with cholesterol, estradiol, estrone, progesterone in olive oil and olive oil alone. With the exception of a very faint erythema and slight induration at the estrone site, all tests were negative at twenty-four and forty-eight hours. It appeared that the skin sensitivity to estrone had been greatly reduced as compared with the original reaction to skin testing.

Case 2.—A married woman, aged thirty-eight, mother of four children, complained of chronic urticaria with premenstrual exacerbations.

There was no history of atopy or previous skin disease, and she had a normal menstrual history. In June, 1943, two months following her last pregnancy, the patient was confined to bed for two months with "migratory rheumatism."

The patient recalled the onset of urticaria on her arms November 18, 1945. The date was associated with sudden cessation of her menses one hour after onset, which occurred on November 16, when she was severely frightened by an accident to her daughter. There was no menstrual bleeding until the following month when her regular period was preceded by dysmenorrhea, low backache, and marked generalized urticaria. Thereafter, the patient had mild urticarial lesions daily, with exacerbations starting ten days premenstrually and improvement with onset of menses. In March, 1946, the premenstrual period was further complicated by nausea and vomiting. Pyribenzamine helped to control the severity of the eruption after two weeks of hospitalization and the care of several physicians had failed to improve her condition.

The patient was first seen on September 12, 1946, at which time she presented a severe urticaria. Tests with endocrine substances were done according to the original intradermal technique (see above), and because of the nonspecific oil reactions the results could not be evaluated. On January 5, 1947, the tests were repeated by the same method, again with unsatisfactory results. The patient offered the information that several days following each of the tests she experienced a slight relief of her urticaria.

On January 20, 1946, the tests were performed with the correct, i.e., our definitive, technique. The twenty-four-hour reading was negative, but the forty-eight-hour reading revealed a questionable reaction to estrone.

On January 27 the tests were repeated on the thighs. The twenty-four-hour reading gave questionable reactions to estrone and progesterone; at the forty-eight-hour reading the previously questionable sites were negative and the estradiol site was positive (3 by 1 cm., erythematous and elevated, with itching). On the following day, January 30, the "recurrent test" was performed by injecting 1 c.c. of estradiol in olive oil subcutaneously. The area of the 1 c.c. subcutaneous injection rapidly became erythematous and edematous, and within one hour generalized urticaria appeared over the body. At the same time the estradiol test site on the right arm from the previous week flared (3 by 2 cm., erythematous and elevated). On the basis of these reactions, hyposensitization was undertaken with the same estradiol solution as used for skin testing.

Treatment was started on February 17, 1947, 0.1 c.c. doses being administered subcutaneously three times weekly for three weeks, with slight improvement of the urticaria. The dose was raised to 0.2 c.c. for another week with continued slight progress. When 0.3 c.c. was administered, the patient suffered her worst flare-up since starting treatment. Two additional attempts to increase the dose from 0.2 to 0.3

TABLE III. CONTROL CASES—PATIENTS WITH DERMATOSES NOT RELATED TO MENSTRUATION OR MENOPAUSE

Dermatosis	Number of Cases Tested	Number of Hormone Sensitive Cases	Hormonal Allergen	Effects of Hyposensitization Therapy	Number of Cases With Questionable Reactions of Any Type
Eczema	23				6
Acne	20				1
Urticaria	7				2
Pruritus vulvae	3				1
Atopic dermatitis	2				
Chronic lichenoid and discoid exudative dermatosis	1				
Pruritus ani	1				
Granuloma annulare	1				1
Axillary folliculitis	1				1
Paronychia	1				1
Undiagnosed	1				

c.c. were each followed by flare-ups of the urticaria. On April 30, following twenty-eight injections of estradiol in olive oil with moderate improvement, we substituted, unknown to the patient, 0.2 c.c. of the olive oil vehicle in place of the estradiol in oil. Both of these substances look identical and were dispensed in identical vials. After one week of such "placebo" treatment, the patient complained of the return of a disturbing degree of urticaria. As a result she remained away from the clinic for one month.

The patient was seen again on June 2, and stated that she had been confined to bed with severe low backache, pelvic pain, and marked urticaria for the two-week period before and during menstruation (the two preceding menstrual periods had caused only moderate exacerbations of the urticaria). Hyposensitization was again started on June 4, using 0.1 c.c. of estradiol in olive oil. The dose was increased to 0.2 c.c. for a total of nine injections, with marked improvement of the patient's urticaria and general symptoms. The dose of estradiol in olive oil was gradually increased to 0.6 c.c., given intramuscularly, for a total of twenty-two injections in this series. In all, a total of fifty injections were given.

Upon completion of this series of injections, on August 11, 1947, the patient was markedly improved, and had only an occasional urticarial lesion. At no time was she denied the use of Pyribenzamine as a means of controlling excessive and intolerable itching. Whereas 400 mg. or more were taken prior to desensitization, only 50 mg. or less were used on completion of therapy. Subsequently the patient had no urticaria and took no Pyribenzamine; her menses were normal and without pain.

On January 26, 1948, we retested the patient with the following steroid hormones in olive oil (as previously used): cholesterol, estradiol, estrone, and progesterone, and with the olive oil vehicle alone. The twenty-four hour readings were negative, as were the forty-eight-hour readings with the exception of a poorly defined, faint erythema (2 by 1 cm.) at the estradiol in olive oil site. At this time a "recurrent test" was done by injecting 1.0 c.c. of estradiol in olive oil, subcutaneously in the right thigh. The patient reported that five hours after the injection, the estradiol in olive oil site began to itch and became intensely red and elevated and was about 1 by 2.5 inches in size. This reaction began to subside in about one-half hour. When seen on the following day, this same site was dusky-red and poorly defined (2 by 5 cm.). The patient did not have any urticaria as a result of the tests.

CONTROL SUBJECTS

Skin tests with the hormone solution were carried out on sixty-four patients who had dermatoses apparently not related to menstruation or menopause (Table III), and who served as controls; thirteen gave questionable

and inconclusive responses of various types. Three were hypersensitive to the olive oil vehicle and were not included in the following statistics. Twelve patients gave questionable reactions to one or more test substances at twenty four hours alone or at both twenty-four and forty-eight hours. There were two patients presenting "retarded reactions." Two patients were tested for the "recurrent test reactions"; one of these, a man aged fifty-three, with an allergic eczematous contact-type dermatitis, gave a questionable positive to androsterone to which he had given a questionable reaction when first tested.

STUDIES WITH VARIOUS OIL SOLVENTS

Because of the difficulty of preparation of the neutralized olive oil, an attempt was made to find another suitable vehicle for testing with steroid hormones. Comparative studies were first made on the relative skin irritancy on cutaneous injection of sterile neutralized olive oil, sterile peanut oil and sterile sesame oil.

Twenty-five unselected patients from among those under treatment in the allergy department of the New York Skin and Cancer Unit were tested with the three oil preparations. An injection of 0.1 c.c. of each oil was given as previously described (at a level somewhat deeper than that usually used for intradermal testing). The tests were read after forty-eight hours with the following results: the neutralized olive oil and the peanut oil produced no reactions, while the sesame oil produced questionable reactions in two subjects. On the basis of these findings, it was decided to try peanut oil as the alternate solvent for the steroid hormones.

Thirty patients who presented dermatoses not apparently related to menstruation or menopause were divided into two groups of fifteen each. One group was tested with cholesterol, estradiol, estrone, and progesterone in olive oil in one arm, and with the same substances in peanut oil in symmetrically situated sites in the other arm. The second group was tested with testosterone, androsterone, and desoxycorticosterone acetate in olive oil and with the olive oil control in one arm, and with the same steroid hormones in peanut oil and with the peanut oil control in symmetrically situated sites in the other arm.

There was no case of sensitivity to olive oil in this group and only one instance of sensitivity to peanut oil, which developed three weeks after the tests were performed. One patient gave a questionable reaction to estradiol in both olive oil and peanut oil at the twenty-four-hour reading. Another gave questionable twenty-four-hour reactions to androsterone and desoxycorticosterone acetate also in both oil solvents. A third patient gave a positive reaction to desoxycorticosterone acetate in the peanut oil solvent.

From these tests we gained the impression that peanut oil solutions of the steroid hormones are suitable for cutaneous testing as far as lack of primary irritancy is concerned. Whether the reaction-producing capacity of olive oil and peanut oil solutions of steroid hormones is identical in patients

with skin hypersensitivity to steroid hormones must still be ascertained in suitable cases.

COMMENT

Dermatoses as related to menstruation and menopause have been reported for many years, but Geber[1] is accredited with first demonstrating experimentally the presence of specific substances circulating in the blood of a patient at the time of the occurrence of menstrual urticaria. Blood serum obtained from a patient at the height of her menstrual urticaria would cause transient urticaria in this patient, but not in other women when injected intravenously during the intermenstruum. This patient could be desensitized by repeated intradermal injections of this serum,[2] whereas such desensitization could not be accomplished by administering the serum of a normal person. Positive skin reactions to extracts of menstrual secretion and probable successful hyposensitization with such extracts were reported by Salen.[6] It is interesting to note that the patient in our Case 1 had once been successfully hyposensitized by a procedure very similar to that used by Salen.

Aside from the work of Zondek and Bromberg, there are only few reports on skin tests for hypersensitivity to steroid hormones. Riebel reported a single case[5] having allergic coryza with premenstrual flare-ups who improved under treatment with folliculin (Theelin) administered subcutaneously, intranasally (nasal spray), or by vaginal suppository. Scratch tests done with folliculin were slightly positive to negative.

Sensitivity to Synapoidin (a combination of chorionic gonadotropin and anterior pituitary follicular stimulating hormone) was elicited by Phillips in a group of patients complaining of premenstrual headache.[4] Positive intradermal tests were reported using 0.02 c.c. of a 1:5 dilution of Synapoidin in 5 per cent glucose. Desensitization was accomplished by repeated intradermal injections of the test solution, gradually increasing the dose to 0.3 c.c. Phillips also found desensitization to be of value in premenstrual tension and premenstrual acne.

Three patients who developed purpura following estrogenic therapy were tested by Watson, Schultz and Wikott.[11] The test consisted of injecting intradermally 0.1 c.c. of 0.2 per cent suspensions of estrone and stilbestrol in physiological saline. The immediate skin test reactions were positive for estrone in one case, stilbestrol in another, and to both in a third case. Passive transfer tests were uniformally negative.

Among our patients complaining of dermatoses apparently related to menstruation or menopause who were tested, postive reactions were elicited in four of thirty-three, i.e., in about 12 per cent of the cases, as compared to 53 per cent with positive reactions in a similar series of dermatoses as presented in the table of the original workers.[13]

Numerous factors, however, must be considered which may account for the rather wide variation in results. In their concluding comment,[13] Zondek

and Bromberg stated: "The high level of the incidence of endocrine allergy in the cases reported above results from case selection and should not be regarded as forming evidence that endocrine allergy is a frequent occurrence. The cases we have described were all selected from a group which had proved resistant to all common methods of treatment, and in which the symptoms of the complaint related to the genital function. For general practice, endocrine allergy is not often encountered." The patients tested in our series, whose complaints were apparently related to genital function, do not fulfill these rigid criteria of selection. Whereas histories were carefully elicited from the patients tested to make certain that the dermatosis was related to menstruation or menopause, it is possible that prolonged study might have revealed some cause unrelated to genital function. Nor had all of our cases run the gamut of common methods of treatment, i.e., we have no proof that they would "have proved resistant to all common methods of treatment."

With the exceptions of the two cases reported above in detail, only skin reactions which we ourselves observed have been included in this report. Yet the statements of patients concerning reactions which they noted leads us to suspect the occurrence in some instances of "retarded reactions" as well as delayed sensitivity to the olive oil solvent. It is possible that had we had the opportunity to follow and retest more of the patients giving questionable reactions, there would have been a higher incidence of subjects in whom hypersensitivity to endocrine substances could have been established.

Moreover, evaluation of the test responses was not always a simple matter, because of the numerous questionable reactions which occurred in the patients presenting dermatoses apparently related to genital function, as well as in the control group. Some of the questionable reactions which occurred despite all precautions taken might be accounted for by the accidental deposition of the test substance in the epidermis and upper cutis, thus causing a nonspecific oil reaction; after 0.1 c.c. of the oily solution was injected and the needle withdrawn, it was not unusual to note a minute backflow of the oil to the surface of the skin. Rubbing of a negative test site, e.g., mechanical irritation of a site caused by a tight dress sleeve, ornamental jewelry, handbag, or packages carried in the arms, in some cases produced a localized erythema which could be misinterpreted for a positive reaction.

Although the factors mentioned may account for some of the questionable or false positive responses, they do not explain all the bizarre reactions which occurred, such as (1) questionable reactions at twenty-four hours with negative reactions at forty-eight hours and with negative "recurrent tests," (2) positive or questionable reactions to olive oil at twenty-four hours, without similar reactions at any of the other sites which had been injected with olive oil containing steroid hormones, (3) the premenstrual flare of several test sites in one of the patients with a dermatitis apparently

related to menstruation, (4) control patients giving "retarded reactions" with a positive reaction at one site and questionable reactions at several other test sites.

We believe that many of the difficulties encountered in evaluating the method of Zondek and Bromberg are due to the use of oil as the vehicle for the steroid hormones. The nonspecific reactions which are inevitably produced when olive oil is injected intradermally necessitated the deposition of the test materials at a deeper level than is customary in orthodox skin testing for the urticarial and tuberculin-type responses. We have used the name "cutaneous" tests since the skin level at which these tests have been performed is neither intracutaneous nor subcutaneous but intermediate between these. The necessity for injecting deeper than usual means a diminished contact of the test materials with the blood vessels and other structures of the upper cutis which may be the principal shock tissue in the orthodox wheal and tuberculin-type responses. Moreover, it stands to reason that the release of the allergenic materials from olive oil solutions takes place at a much slower rate than the release of allergenic materials from aqueous solutions. Obviously these factors can account not only for some of the difficulties encountered in the evaluation of the responses elicited but, perhaps even more important, the type of response seen in these tests. For the reactions, described by Zondek and Bromberg in a large series of cases and confirmed by us in a few dermatologic cases, do not fit in with any of the classical immunologic skin responses, i.e., the urticarial, tuberculin-type and eczematous reactions. Rather these responses are either a type of skin response not hitherto described or they are a type of response which is intermediate between the urticarial *and* the tuberculin-type responses. Our limited experience with positive reactions in these tests leads us to believe that this is not an entirely new type of cutaneous reaction but only a "crossing" between the urticarial and tuberculin-type responses, due to the use of oil as the vehicle for the allergen and the deposition of the allergenic materials relatively deep in the skin.

In our clinical material of dermatologic cases "related to genital function," the tests for hypersensitivity to endocrine substances led to positive results in only a few cases. Based on these results this new method would not appear to be promising as a *routine* investigative procedure for large series of cases. However, the positive test results observed in a few cases and the encouraging results of specific therapy, instituted in two cases on the basis of the test results, indicate that the method of Zondek and Bromberg deserves further trial in properly selected cases.

SUMMARY AND CONCLUSIONS

1. Cutaneous tests for hypersensitivity to steroid hormones according to the method of Zondek and Bromberg were performed in 102 dermatologic patients.

2. Among the thirty-eight patients whose dermatoses were apparently

related to genital function (menstruation, menopause) there were four who gave positive skin responses. In two of these (both cases of urticaria) hyposensitization was carried out with the hormone which had elicited the positive skin response and and was followed by very marked clinical improvement. In eleven additional patients questionable and inconclusive responses were elicited.

3. Among the sixty-four control patients whose dermatoses were *not* related to genital function, no positive skin reactions were seen. In thirteen of these patients questionable and inconclusive responses were elicited.

4. Screening tests suggested that it may be possible to substitute peanut oil for the specially prepared olive oil as a vehicle for the steroid hormones.

5. The skin responses elicited in these tests were different from the classical types of immunologic skin reactions, and suggest a form of response intermediate between the urticarial and tuberculin-type response. This unusual type of skin response is attributed to the use of oil as a vehicle and to the relatively deep deposition in the skin of the test materials.

6. Tests for hypersensitivity to steroid hormones (method of Zondek and Bromberg) are, in our opinion, not suitable for routine diagnostic use. However, in a certain number of carefully selected cases, related to genital function, this method has definite merits. Hyposensitization in urticaria cases with positive tests to steroid hormones is a promising procedure.

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FEVER DUE TO FOOD ALLERGY

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THIS paper reports food allergy as one cause of "unexplained fever."* Fever due to drug and serum allergy is generally recognized. Very occasionally, fever also arises from allergy to pollens or other inhalants, as reported by Rowe[13,18] and Urbach. Though fever due to food allergy was first reported by Barnathan[2] in 1911 and by Laroche, Richet, and Saint-Girons[9] in 1919, and has been reported by other observers[1,5-8,18,19] since then, its general recognition has been too long delayed.

Failure to recognize food allergy as one cause of fever accounts for some unjustifiable diagnoses of idiopathic or psychogenic fever, subclinical tuberculosis, brucellosis or other questionable infections. It has led to unnecessary operations on tonsils, appendices, gall bladders and pelvic organs. Needless surgical intervention has been performed on nasal sinuses because of the association of fever with nasal congestion, blocking or postnasal mucus, and especially with swollen membranes or opacities in the antra or other sinuses which were not due to infection but to allergy, especially to foods. Such fever often has constituted the chief reason for prolonged, unnecessary inactivity or vacations, for bed rest in hospitals or sanitaria, and for extensive clinical and laboratory investigations.

The following case report illustrates the occurrence of prolonged allergic fever that was preceded by a life-long anorexia, aversion for milk, and recent colonic symptoms due to food allergy. Because of this fever, the patient was hospitalized for four and one-half months; during this time many laboratory and clinical investigations were conducted, and at one time a presumptive diagnosis of psychogenic fever was made. This case is of special interest because in the record is contained the only chart of a course of fever due to food allergy that as yet has been published.

CASE REPORT

A girl, aged eighteen, developed fatigue and anorexia in July, 1942. Gradually, intermittent cramping arose in the mid-abdomen and rectum. By the middle of August there was watery diarrhea with afternoon fever and an elevation in temperature to 102° F. The administration of succinyl sulfathiazole for two weeks had no effect on the fever. On September 19, she was then hospitalized and her problem studied for about a month. Proctoscopic examinations revealed an easily bleeding and slightly inflamed mucosa. Laboratory studies and physical examination (Table I) revealed no cause for the continued fever. She was sent, on October 12, to another hospital where she remained for three and one-half months at complete rest. Figure 1 shows the frequency, variation and degree of temperature that was associated with the fever. In the four and one-half months of hospitalization, she passed from one to four stools a day; these were soft and at times semi-fluid.

*Hypothermia also results from allergy, especially during anaphylactic shock.

TABLE I. SUMMARY OF PREVIOUS TREATMENT AND LABORATORY STUDIES IN CASE ONE

Stools were soft or liquid, 1 to 3 a day during hospitalization.
Pulse rate varied in the morning between 75 and 90 and in the afternoon between 110 and 130 when fever was present.
With the control of food allergy, the afternoon pulse rate fell to 90 to 100.
Vitamin B complex was given subcutaneously, 1 to 2 c.c. every two days.
Sulfadiazine, 6 gm. daily, was given from November 23, to December 6. (Blood level, 12.6 mg. per cent.)
Aspirin, 10 gm. twice daily, was given from December 31 to January 27.

BLOOD COUNTS

Date	Hemoglobin (Method?)	Red Cells x 1000	White Cells	Total Polymorphonuclears	Differential, PMN's		Lymphocytes	Large Mononuclears	Eosinophiles	Basophiles
					Banded	Segmented				
9-20-42	69	4250	9100	84			14		2	
10- 6-42	71	3960	7600	81			14	3	2	
10-15-42	79	4900	8500	52	44	8	37	8	2	1
10-30-42	71	4260	8100	61	33	28	18	7	13	1
11- 4-42	71	4460	7500	65	43	22	18	9	6	2
11-12-42	71	5000	6900	65	56	9	22	3	9	1
11-18-42	74	5150	9250	57	42	15	24	9	10	
11-23-42	76	5300	10470	67	51	16	20	3	10	
11-27-42	76	5300	7350	74	58	16	14	6	6	
12- 7-42	83	4900	4800	58	48	10	24	8	10	
12-14-42	78	5300	5200	59	40	19	22	5	12	2
12-31-42	73	4910	4570	64	60	4	18	7	9	2
1-19-43	64	4900	5700	54	40	14	27	5	14	
1-25-43	90	5340	6400	41	18	23	27	9	23	
2- 8-43	70		5850	55	22	23	30	8	7	
2-15-43	68		5400	60			25	9	4	2
5-19-43	70	5190	6750	72			20	5	2	1

LABORATORY STUDIES

Urine analyses: 10 complete ones, negative.
Stool culture (9-21-42): negative.
Blood culture (9-21-42): negative.
Stool examination for ova and parasites: negative.
Blood examination for malaria: negative.
Tuberculin, 1-2,000 O.T.: negative.
Coccidioidin skin test, 1-100: negative.
Serum agglutination tests for typhoid, paratyphoid A and B, brucella on three occasions were negative; for abortus, S. Supestifer, on two occasions were negative. Complement fixation test for brucella was negative.
Heterophile agglutination: negative.
X-ray of chest and sinuses: negative.
X-ray of colon: negative.

Sedimentation Rates:
9-20-43—30 minutes—18 mm.
10- 1-43—37 minutes—18 mm.
10-14-43—60 minutes—25 mm. (normal 10)
7- 2-44—60 minutes—10 mm.

Vitamin B complex, 1 to 2 c.c., was injected intramuscularly every two days during most of this period. Sulfadiazine, 6 gm. daily, was given from November 25 to December 6, with no definite effect on the fever. Finally, aspirin, 10 gr. two times a day, was given from December 31 to January 27, and resulted in intermittent lowering of the fever. Throughout her entire illness, when her temperature was elevated above 101° F. and especially over 102.5° F., there was at times chilling with "goose flesh" reactions. There were night sweats which varied with the amount of fever. However, no headache or generalized aching occurred. In November a small fissure was discovered at the posterior commissure of the anal aperture, and later an induration, 2 by 4 cm., was discovered in the left wall of the lower rectum. This was incised on December 11, but produced no reduction in the fever.

The patient was referred to the writer by Dr. Karl F. Meyer on January 29, 1943. Food allergy, especially for milk, was suspected immediately for the following reasons: the patient stated emphatically that she never had liked milk. It had been forced upon her in childhood and since then had been taken only when flavored, or in ice cream, sherbets or in cooking. The patient, according to her mother, always

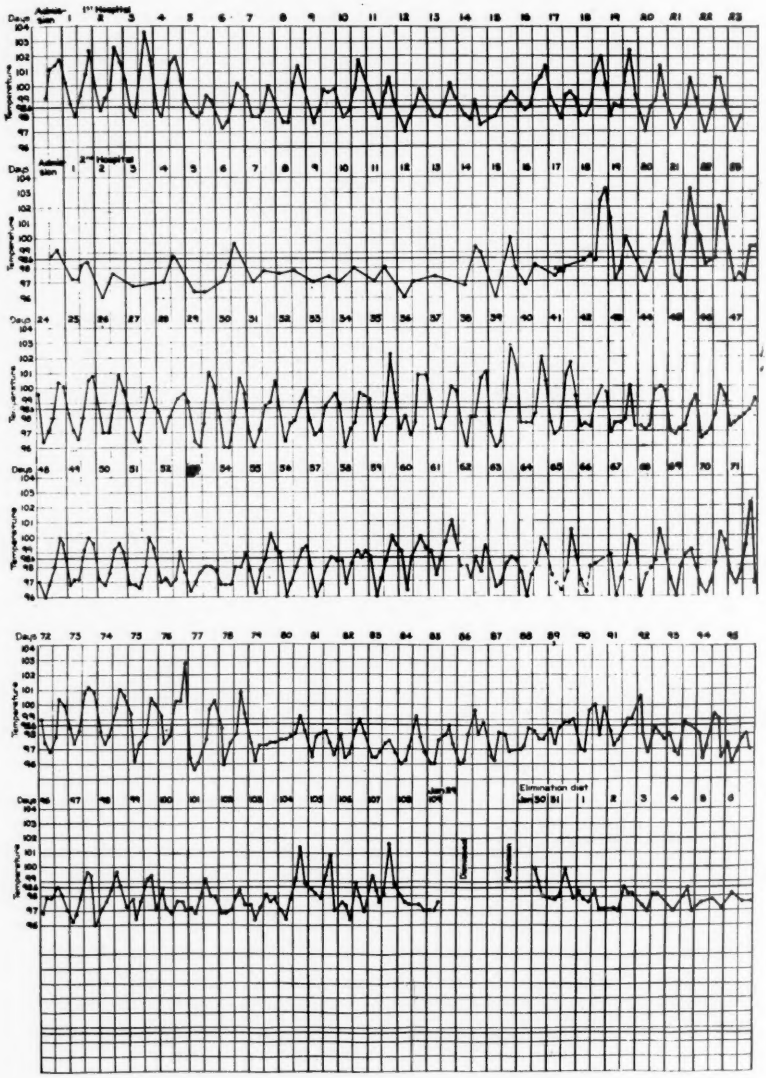

Fig. 1. Temperature chart in three hospitals.

had been finicky about her food; she had been spoon-fed entirely up to the age of six years. Until this time all foods apparently had agreed with her. During the hospitalization for four and one-half months, the mother had spoon-fed her on most evenings because of anorexia; several glasses of milk, cream and butter in desserts and cooking had been included in her daily diet. With the exception of a

life-long lack of appetite and energy, the patient gave no previous history of gastrointestinal symptoms nor of any other allergic manifestations or chronic illness. There was no familial history of allergy.

The following reactions were obtained with the scratch test with eighty-five food allergens: coconut 2-plus; peanut 2-plus; pecan 1-plus; black walnut 1-plus; English walnut 1-plus. With the intradermal test, the following reactions occurred: wheat, coffee, and peach gave questionable reactions; string beans 2-plus; tomato 2-plus; white potato 2-plus; prune 1-plus; grapefruit 1-plus. It is of interest that the scratch and intradermal tests with milk were negative.

Because of the possibility that the fever, fatigue, colonic symptoms, the long standing finickiness for foods and anorexia were due to food allergy, she was placed on the writer's cereal-free elimination diet.[18] As may be seen in the chart, her fever disappeared in twenty-four hours. During the next four days she was allowed to increase her activity, and in one week she walked out of the hospital, fever-free and symptom-free. Her appetite and energy gradually increased, to become greater than at any time in her life. In three weeks her weight had increased from 108 to 119 pounds, and in three more weeks she weighed 124 pounds. In the next five months all foods, one by one, were added. On February 26, she drank 1 ounce of milk and increased the amount to 2 ounces on the next day. On the third day her abdomen felt full and distended, and her anal tissues were sore and inflamed. That evening, for the first time since the second day of the elimination diet, her temperature was 99° F., and the following evening it was 99.2° F. The abdominal and anal distress gradually disappeared during the next seven days. Since then, similar symptoms and mild fever have reappeared when milk, even in small amounts as in a doughnut or candy, has been ingested. Chocolate, to a lesser degree, causes the fever and colonic distress. By August her weight had increased to 132 pounds. At present, in 1948, she still cannot tolerate milk without resultant fever and rectal and anal distress. She is well and free of fatigue and weighs 136 pounds.

When the writer first saw the patient there was a muco-purulent discharge from the anus. Proctoscopic examination revealed an ulcer about 1 inch in diameter at the anorectal margin. The ulcer was removed by surgical procedure and was followed by rapid healing. In spite of the ulcer, her temperature remained normal as long as the allergenic foods were absent from the diet.

The allergic fever was of the persistent type and was present daily during her four and one-half months of hospitalization, except for twelve days during the first two weeks in the second hospital and again for twelve days on and off during the last twenty-nine days in the hospital. As will be discussed later, temporary refractoriness or desensitization best explains the first period of normal temperature. The effect of aspirin, 10 grains twice a day, given from the seventy-nineth to the one hundredth and ninth day, probably accounts for intermittent normal temperature in the latter period. It is interesting that the morning temperature failed to fall to 97° F. during the first nineteen days, in comparison to its frequent fall to 97° F., and even to 96° F., thereafter. Since the relief of her food allergy, the morning temperature has not been below 97° F.

DISCUSSION

Milk allergy was the main cause of the allergic fever and the colonic and anal allergy. Chocolate seemed to be a minor cause. Peanuts and walnuts caused moderate colonic distress. Milk is the food which probably is the most frequent cause of allergic fever and is a common cause of gastrointestinal allergy,[16] especially in the colon.[17] Other foods always must be suspected, particularly those excluded from the writer's elimination diets.

The life-long history of aversion to milk in this patient emphasizes the importance of a carefully recorded dietary history. Although allergy is not always responsible for food dislikes and disagreements, such history always requires the proper study of food allergy. Because of the frequency of food allergy, a dietary history indeed should be routine in practice.

The fallibility of the skin test,[15,20] especially for food allergy, is illustrated by several positive reactions which caused no clinical symptoms and the negative reaction to milk, even intradermally, which caused such definite allergy in this patient.

Because of this fallibility of the skin testing and the usual allergy to more than one or two foods, the writer's usual routine is to study with his elimination diets[18] those patients who are suspected of having food allergy; this is modified by a history of definite food disagreements or dislikes and by positive reactions to foods obtained by the scratch method. Thus, in this patient, the writer's cereal and fruit-free elimination diet was utilized. Fruit was excluded since it is a common cause of allergy in all parts of the gastrointestinal tract. When the fever and the colonic symptoms in this patient had been absent for two weeks, other foods were added, each being tried for three or four successive days before another was added. With the inclusion of milk, the fever and colonic symptoms recurred, as noted above. Peanuts, walnuts and chocolate also produced colonic distress and moderate diarrhea.

During this period of study of possible food allergy, the total elimination of excluded foods is required because a maximum degree of allergy always must be assumed until the symptoms are relieved. Then the degree of allergy to the causative foods can gradually be determined by feeding tests. Thereafter, partial or total exclusion of the food can be continued as required for relief. The maintenance of nutrition, while the elimination or any trial diet is being used, has long been emphasized by the writer because of the necessity to use the diet for more than a few days in most cases and the usual necessity for subsequent elimination of proven allergenic foods for months or years to obtain relief of symptoms. Prolonged diet trial is especially necessary for the study of food allergy as a cause of cyclic recurrent manifestations with intervening days or weeks of freedom.

The persistent allergic fever, in this case, disappeared in two days after the elimination of the allergenic foods, which is in contrast to the less rapid disappearance of such fever in other similar patients studied by the writer. This varying speed of relief of fever and other manifestations of food allergy may depend on the persistence of the specific reacting bodies or of the food allergens in the blood and tissues after the total elimination of the allergenic foods. Moreover, the cellular and tissue changes resulting from the specific allergic reactions require varying times for restitution to normal after the proper diet has been instituted.

In contrast to the persistent type of fever which usually results from

food allergy, the writer soon will report the recurrent allergic fever which may occur with cyclic attacks of bronchial asthma or symptoms of gastrointestinal allergy and less often with other recurrent manifestations of food allergy. The normal temperature between these periods of recurrent allergic fever is comparable to the relief of other symptoms after recurrent attacks of other allergic manifestations, including bronchial asthma, allergic headache, symptoms of gastrointestinal allergy, intermittent hydrarthrosis, or other cyclic manifestations of food allergy. The allergenic food or foods usually are common ones eaten every day. The duration and severity of the fever or other symptoms probably depend on the accumulation of the specific reacting bodies in the cells of the shock tissues and their exhaustion during the reactive period. Persistent fever and other symptoms due to food allergy, on the contrary, may be attributed to the failure of the shock tissues to become desensitized or refractory to the causative allergens.

Chilling and goose flesh with rising fever and night sweats upon retiring or through the night often occur from food allergy. Children with allergy may perspire soon after retiring, especially over the head and neck, even when lightly covered. Night sweats due to chronic food allergy and not accompanied by fever in children and adults have been observed by the writer.

Food allergy should be considered as a cause of fever when the physical examination and laboratory studies give no explanatory clues, and especially when treatment based on positive findings gives no relief. As in other possible clinical allergy due to food, this study is especially necessary if the patient has a personal history of other allergic manifestations and/or a familial history of allergy. Thus, in this case, the aversion to milk and the probable colonic allergy stressed the study of food allergy as one cause of the fever. The fever may be of major or minor consequence. The absence of any familial allergy did not detract from this necessity.

During the four and one-half months before the writer saw the patient, infections of all types had been sought for as evidenced by the many blood counts, agglutination tests, blood cultures, stool examinations and other tests recorded in Table I. The absence of leukocytosis or of an increase in the polymorphonuclear cells, except in the first two counts, is to be noted, though leukocytosis may occur, especially in children with uncontrolled allergy. The rapid sedimentation rates, apparently due to food allergy in this patient, are of interest. The tendency to an increasing blood eosinophilia should have suggested allergy in this patient. With control of the food allergy, the eosinophilia and rapid sedimentation rate disappeared. Trichinosis also had been considered because of the eosinophilia.

The relief from her fever, from the colonic and anal symptoms, and from the fatigue and the other toxic symptoms by use of the elimination diet, and their subsequent reproduction by the ingestion of milk, prove

that food allergy was responsible. Her initial colonic symptoms suggested the onset of a possible chronic ulcerative colitis, which, in the writer's opinion, is frequently due primarily to food allergy[17] (several cases due to pollen allergy also have been studied). The easy bleeding and mild inflammation of the mucosa, however, only were demonstrated during several proctoscopic examinations. The recurrence of the colonic and anal distress on a few occasions when milk has been taken since the original control of her allergic fever five years ago, emphasizes the persistence of the allergic reactivity in these tissues. If the allergy had not been recognized, more definite tissue changes due to chronic ulcerative colitis might have developed.

As soon as the allergic fever and the colonic and toxic symptoms[10,11,12,14] were relieved with the elimination diet, the patient for the first time in her life ate with avidity and willingness and evidenced normal energy, enthusiasm and nervous stability. It is noteworthy that a steady gain of weight up to 26 pounds in the first six months of allergic supervision occurred with an entirely milk-free diet. In this patient anorexia was due in food allergy alone.† Milk was excluded from the diet without nutritional damage inasmuch as calcium was given and an adequate protein and caloric intake were maintained.

The most likely explanation of allergic fever is a disturbance in the temperature-regulating center of the brain by a localized or generalized allergic reaction. The following less likely possibilities may be mentioned. The allergic reaction in the shock tissues might produce fever. Again, the allergic reaction in nasal, bronchial or gastrointestinal mucosa, especially if severe and explosive in type, might encourage the rapid growth of otherwise quiescent bacteria. The rapid relief of fever in this patient with the exclusion of milk rules out infection as a cause.

CONCLUSIONS

1. Food allergy as one cause of "unexplained fever" must be recognized. Although any food may be responsible, milk is the common offender.
2. Failure to consider allergic fever accounts for needless surgical operations performed because of possible foci of infection or other lesions, and also for the unnecessary bed rest in home, hospital, or sanitarium.
3. Other manifestations of food allergy of varying severity may accompany allergic fever.
4. Chilling and night sweats often occur. Nights sweats, moreover, may result from chronic food allergy in the absence of allergic fever.
5. Leukocytosis, eosinophilia and a rapid sedimentation rate may or may not be present.
6. Allergic fever due to food allergy may occur in recurrent attacks; usually it is persistent and somewhat varying in degree.

†Chronic food allergy is a common cause of anorexia, not only in children but also in adults.

7. One case of fever due to food allergy associated with allergic toxemia and colitis, with the recorded temperature during hospitalization for 122 days before allergy was suggested as one possible cause, is reported and discussed. This graphic record of prolonged fever due to food allergy is the first of its kind in the literature.

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MOLD DISTRIBUTION IN AIR AND DUST IN KENTUCKY

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EXCEPT for the survey made in Louisville, Kentucky, by the Committee on a Pollen Survey of the United States for the Society for the Study of Asthma and Allied Conditions in 1942 (Vander Veer et al[28]), no extensive studies of mold distribution in Kentucky have been reported. A survey has been made, therefore, of the distribution of molds in outdoor air, indoor air, and in house dust, in eastern Kentucky and in central and western Kentucky.

Two quantitative surveys were made, one in January and the other in March.

For the primary isolation of the molds, the plate method with Anderson's[1] modification of Sabouraud's medium was employed, except that the medium was adjusted to the desired pH (3.0) with N/1 H_2SO_4 instead of N/1 HCl, after sterilization in the autoclave.

Dehydrated Bacto-potato-dextrose agar, adjusted to pH 5.6, was used for subculturing the molds from the plates and for maintaining stock cultures of the isolates.

Poured plates of the above plating medium, which had been sealed with scotch tape until ready for use, to prevent drying, were exposed on the same day in each of the following places: Ashland, Catlettsburg and Middlesboro in eastern Kentucky; Covington, Independence, Lexington, Nicholasville and Coakley in central Kentucky; and Kevil in western Kentucky. On January 1, 1946, co-operators at each location away from Lexington, and we in Lexington, exposed one plate outdoors and one plate indoors for fifteen minutes. The plates were resealed with scotch tape and the ones away from Lexington were returned on January 3. On January 1 each co-operator, as well as we in Lexington, also collected a sample of house dust in a sterile test tube.

All the exposed plates were incubated at room temperature for from three to seven days. Each sample of house dust was plated on Sabouraud's medium by streaking the plates with a loopful of the dust. These plates were also incubated at room temperature for from three to seven days.

The colonies of each type of mold, as determined by macroscopic appearance, were counted, and a representative of each type was subcultured on potato-dextrose agar slants. Two sets of stock cultures were made from each type.

For the identification of the molds, moist chamber preparations of the

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organisms, incubated at room temperature, were studied daily under the 16 mm. and 4 mm. objectives of the microscope.

The identification and classification of the cultures were made in accordance with the criteria set forth in Gilman's *Manual of Soil Fungi*.[13]

The survey in March was carried out in the same manner as the one in January, except that Pikeville, in the eastern part of the state, was included in the survey.

Table I shows the results of the January survey. Representatives of the following genera of molds were found: *Alternaria, Aspergillus, Cephalosporium, Hormodendrum, Penicillium, Phycomyces, Rhizopus,* and *Tilachlidium.* The species of the genus *Penicillium* were the most widely distributed and the most numerous. Only a few of the species of this genus were identified. These were *Penicillium citrinium, Penicillium frequentans, Penicillium notatum,* and *Penicillium spinulosum.*

Other species of the *Fungi Imperfecti* that were identified were *Alternaria geophilia, Alternaria humicola, Alternaria tenuis, Aspergillus luchuenis, Aspergillus versicolor, Cephalosporium acremonium, Hormodendrum cladosporioides, Hormodendrum nigrescens,* and *Hormodendrum olivaceum.* Of these, *Aspergillus luchuenis* and *Hormodendrum nigrescens* were the most numerous and the most widely distributed.

The only species of the *Phycomycetes* that was identified was *Rhizopus nigricans.*

Table II shows the results of the March survey. In addition to all the genera of molds found in January, *Macrosporium, Monotospora, Mucor, Oospora, Stemphylium* and *Tetracoccosporium* were also found. Members of the *Penicillium* genus were again the most widely distributed and the most numerous.

The following species of the *Fungi Imperfecti* were identified: *Alternaria humicola, Alternaria tenuis, Aspergillus fumigatus, Aspergillus luchuenis, Aspergillus niger, Aspergillus veriscolor, Aspergillus tamarii, Cephalosporium acremonium, Hormodendrum cladosporioides, Hormodendrum hordei, Hormodendrum olivaceum, Hormodendrum viride, Macrosporium commune, Monotospora brevis, Oospora variabilis, Penicillium citrinium,* and *Stemphylium macrosporoideum.*

Mucor piriformis, Rhizopus nigricans, and unidentified species of *Mucor* and *Phycomyces* represented the *Phycomycetes.*

Of the species identified, the most important, from the standpoint of distribution and numbers, were *Alternaria tenuis, Aspergillus luchuenis,* and *Hormodendrum cladosporioides.*

In Figure 1, parts of the data from Tables I and II have been summarized to show a comparison of the results of the January and March surveys in eastern Kentucky. The March survey yielded a higher percentage of *Aspergillus, Hormodendrum,* and *Tilachlidium,* a lower percentage of *Penicillium,* and an equal percentage of *Cephalosporium. Oospora, Mucor, Rhizopus, Tetracoccosporium, Alternaria, Macrosporium,*

TABLE I. DISTRIBUTION OF MOLDS IN OUTDOOR AIR, INDOOR AIR, AND HOUSE DUSTS IN KENTUCKY DURING JANUARY, 1946

Molds	Ashland (NE)			Catlettsburg (NE)			Middlesboro (SE)			Coakley (SC)			Covington (NC)			Independence (NC)			Lexington (C)			Nicholasville (C)			Paris (C)			Kevil (W)			Totals
	1*	2†	3‡	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Alternaria geophilia																				6											6
humicola																			12	28			6		1						40
tenuis																															7
Sp.																															0
Aspergillus fumigatus																															0
glaucus group																						3									3
luchuenis									13			1			4			10			42		1	5					1		77
niger																															0
versicolor												2									38						4				44
tamarii																															0
Sp.											6																			1	7
Cephalosporium acremonium									1			1		1		3															6
Hormodendrum cladosporioides					2						1			6	5	2					2										18
hordei																															0
nigrescens	2	1									9												51								66
olivaceum																1															1
viride																															0
Macrosporium commune																															0
Monotospora brevis																															0
Mucor piriformis																															0
Sp.																															0
Oospora variabilis																															0
Sp.																															0
Penicillium citrinium								6		3			3	1																	13
frequentans																			16	13	7										36
notatum																							10								10
spinulosum																3															3
Sp.				15	7	21	49	31	61	1	14	-	38	39	18	17		65	13	32			10	11	1	3			2	121	569
Phycomyces sp.			13						1					3				26			5			6							54
Rhizopus nigricans																					3										3
Stemphylium macrosporoideum																															0
Tetracoccosporium sp.																															0
Tilachlidium sp.		4																													4
Unidentified				1	1						2					2		1											1		8
Totals	2	5	13	16	10	21	49	37	76	4	32	4	41	50	27	28	0	102	41	79	97	3	81	22	2	3	4	0	4	122	975

*Number of colonies found on plates exposed outdoors for fifteen minutes.
†Number of colonies found on plates exposed indoors for fifteen minutes.
‡Number of colonies found on plates streaked with one loopful of house dust.

TABLE II. DISTRIBUTION OF MOLDS IN OUTDOOR AIR, INDOOR AIR, AND HOUSE DUSTS IN KENTUCKY DURING MARCH, 1946

†Number of colonies found on plates exposed indoors for fifteen minutes.
‡Number of colonies found on plates streaked with one loopful of house dust.

TABLE II. DISTRIBUTION OF MOLDS IN OUTDOOR AIR, INDOOR AIR, AND HOUSE DUSTS IN KENTUCKY DURING MARCH, 1946

Molds	Ashland (NE)			Catlettsburg (SE)			Middlesboro (SE)			Pikesville (E)			Coakley (SE)			Covington (NC)			Independence (NC)			Lexington (C)			Nicholasville (C)			Paris (C)			Kevil (W)			Totals
	1*	2†	3‡	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Alternaria geophilia																																		0
humicola																						10		7							4			21
tenuis	3							1		4						2			1			8	13	6				3	2			3		46
Sp.																2													2		5			9
Aspergillus fumigatus													30																					30
glaucus group																																		0
luchuenis			3											4				5						5			10			16				43
niger												3		3				2					7										2	17
versicolor		1																	1	12	8													22
tamarii						9																												9
Sp.		13											31																	12				56
Cephalosporium acremoniu m								1						5												10								16
Hormodendrum																																		
cladosporioides			6										3		6			20						8			34			27				104
hordei																8																		8
nigrescens																																		0
olivaceum								2														12	3											17
viride				9															6				4					5						24
Macrosporium commune				2																														2
Monotospora brevis																									5									5
Mucor piriformis						5																												5
Sp.												5																					4	9
Oospora variabilis							3			7	2																	2						14
Sp.		3													14																	1		18
Penicillium citrinium									13															16										29
frequentans																																		0
notatum																																		0
spinulosum																																		0
Sp.	12				5	23		30			1			33			6	10		9	4		20			7	38					13	6	217
Phycomyces sp.																				1														1
Rhizopus nigricans									8															3			10			3				24
Stemphylium																																		
macrosporoideum				2																														2
Tetracoccosporium sp.						3																												3
Tilachlidium sp.	7														3																		3	13
Unidentified			1		1			1		2	1		2	1		1									1			2	1		1			15
Totals	22	17	10	13	6	40	3	35	21	13	4	8	5	100	30	13	6	37	8	22	12	30	47	45	6	17	92	12	5	58	10	17	15	779

*Number of colonies found on plates exposed outdoors for fifteen minutes.
†Number of colonies found on plates exposed indoors for fifteen minutes.
‡Number of colonies found on plates streaked with one loopful of house dust.

and *Stemphylium* were found only in March, while *Phycomyces* was found only in January.

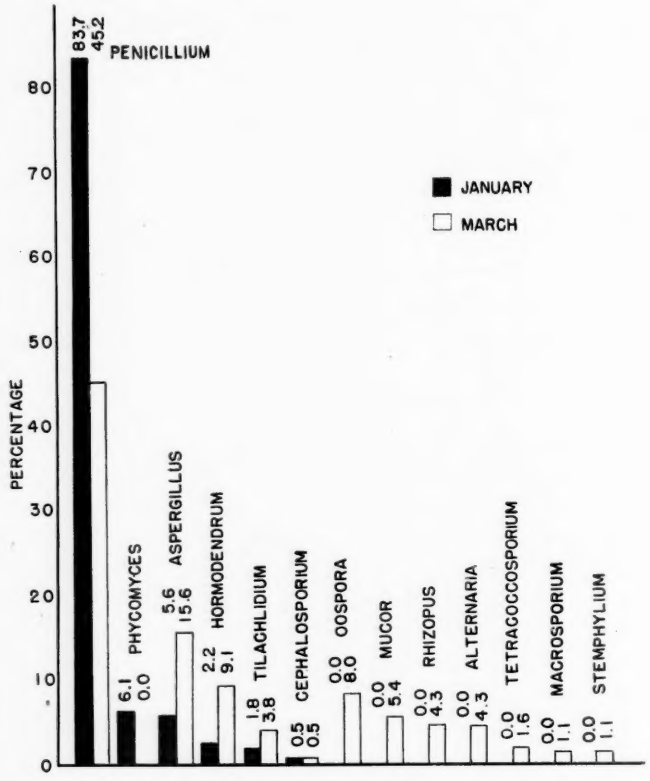

Fig. 1. Comparison of genera of molds found in eastern Kentucky during January and March, 1946.

In Figure 2, parts of the data from Tables I and II have been summarized to show a comparison of the results of the January and March surveys in central and western Kentucky. In this section, too, the March survey yielded a lower percentage of *Penicillium* and *Phycomyces* and a higher percentage of *Aspergillus* and *Hormodendrum*. It also yielded a higher percentage of *Alternaria, Cephalosporium, and Rhizopus*. The March survey yielded a wider variety of molds. In addition to all the genera found in January, *Oospora, Tilachlidium, Monotospora,* and *Mucor* were also found.

If Tables I and II are referred to again, it will be seen that certain species of molds were found entirely in March, others almost entirely in

March and one species only in January. *Hormodendrum hordei, Hormodendrum viride, Aspergillus fumigatus,* and *Aspergillus niger* were found

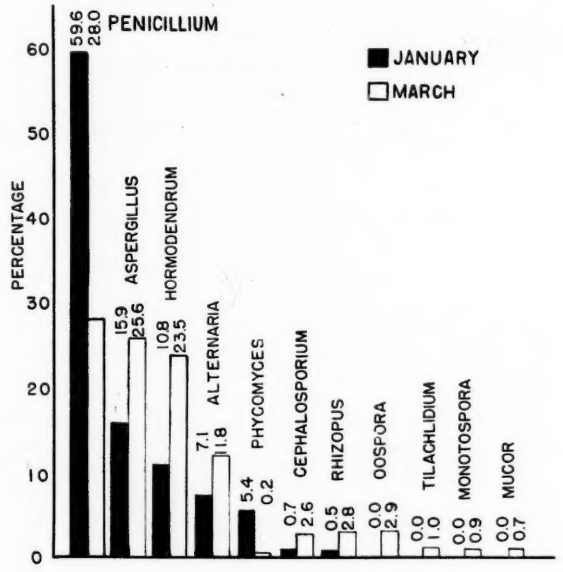

Fig. 2. Comparison of genera of molds found in central and western Kentucky during January and March, 1946.

entirely in March. *Hormodendrum cladosporioides* and *Alternaria tenuis* were found almost entirely in March while *Hormodendrum nigrescens* was found only in January.

In Figure 3, parts of the data from Tables I and II have been summarized to show the comparison of the results of the surveys in central and western Kentucky with the results of the surveys in eastern Kentucky. Central and western Kentucky yielded higher percentages of *Aspergillus, Hormodendrum, Alternaria, and Cephalosporium,* while eastern Kentucky yielded higher percentages of *Penicillium, Oospora, Tilachlidium,* and *Mucor. Phycomyces* and *Rhizopus* were approximately equally prevalent in the two localities. *Tetracoccosporium, Macrosporium,* and *Stemphylium* were found only in eastern Kentucky; *Monotospora,* only in central and western Kentucky.

Penicillium was found to be the most prevalent mold genus throughout the state.

The list of genera found in Kentucky does not differ materially from those reported from other sections of the country. Table III lists the surveys of air-borne molds that have been made in the United States. The

localities in which the surveys were made, the year, the investigators, and the molds found are recorded. Table IV lists all the mold genera that have been reported in these surveys and the number of investigators by

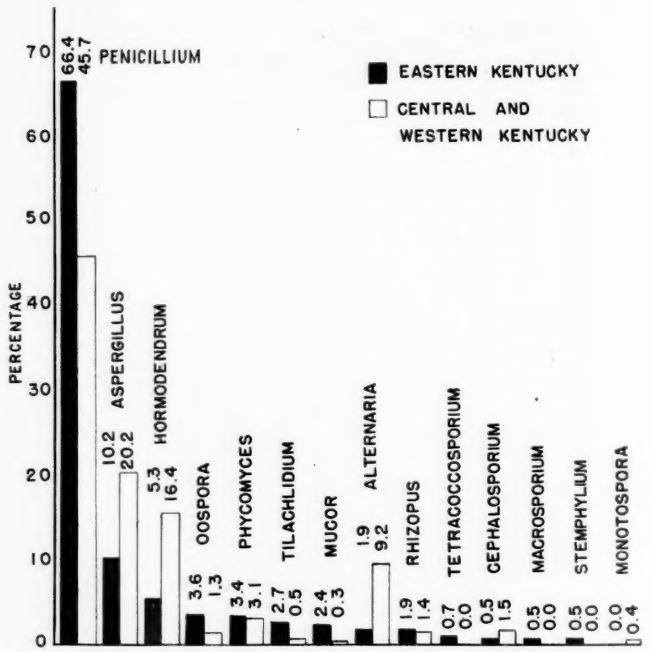

Fig. 3. Comparison of genera of molds found in eastern Kentucky with those found in central and western Kentucky during January and March, 1946.

whom they were reported. Listed in this table also, for comparison, are the mold genera found in our survey in Kentucky. It may be seen from this table that of the genera reported in other parts of the country, we failed to find *Monilia, Trichoderma, Helminthosporium, Cladosporium, Monosporium, Fusarium, Chaetomium, and Spondylocadium.* Of greater significance, perhaps, is our finding of four genera that had not been reported from any of the other sections of the country. These genera are *Monotospora, Stemphylium, Tetracoccosporium,* and *Phycomyces.*

In Table V the data have been summarized to show the distribution of molds in outdoor air, indoor air, and house dusts. *Alternaria* was found most frequently in outdoor air, comprising 17.8 per cent of the total molds from that source, 10.6 per cent of those from indoor air, and only 1.5 per cent of those from house dusts. *Aspergillus* was found most frequently in house dusts, comprising 23.9 per cent of the total molds from that source, 17.5 per cent of those from indoor air, and only 1.3 per cent of

TABLE III. SURVEYS OF AIR-BORNE MOLDS IN THE UNITED STATES

Locality	Year	Investigator	Molds Found
Baltimore, Md.	1932	Patterson and Gay[19]	Mucor, Rhizopus, Penicillium, Aspergillus
Oklahoma	1932	Balyeat, Stemen, and Taft[2]	Aspergillus, Penicillium
Galveston, Texas	1934	Prince, Selle and Morrow[23]	Monilia, Penicillium, Aspergillus, Trichoderma, Helminthosporium, Cladosporium
Boston, Mass. up to 19,600 ft. (aeroplane)	1934	Proctor[24]	Aspergillus, Penicillium, Cladosporium, Alternaria, Helminthosporium, Monilia, Trichoderma
Boston, Mass. up to 20,000 ft. (aeroplane)	1935	Proctor[25]	Aspergillus, Penicillium, Rhizopus, Mucor, Oospora, Monosporium, Macrosporium, Tilachlidium, Fusarium
Chicago, Ill.	1936	Feinberg[11]	Aspergillus, Penicillium, Alternaria, Hormodendrum
Chicago, Ill.	1936	Feinberg and Little[12]	Alternaria, Penicillium, Aspergillus
Washington, D. C.	1936	Brown[6]	Alternaria, Aspergillus, Penicillium
Wheat belt	1937, 1938	Durham[8, 9]	Alternaria, Hormodendrum
Coastal areas of Texas	1937	Prince and Morrow[22]	Monilia, Penicillium, Aspergillus, Trichoderma, Helminthosporium, Hormodendrum, Cladosporium
New England	1938	Pratt[21]	Alternaria, Hormodendrum, Aspergillus, Penicillium, Chaetomium
Pacific Northwest	1938	Schonwald[26]	Alternaria, Aspergillus, Hormodendrum, Trichoderma, Mucor, Rhizopus
Ann Arbor, Mich.	1939	Biggs and Sheldon[5]	Alternaria, Hormodendrum, Penicillium
Cincinnati	1939	King[17]	Alternaria
Iowa	1939	Halpin[14]	Alternaria, Hormodendrum
Seattle and vicinity	1940	Stroh[27]	Hormodendrum, Alternaria, Aspergillus, Cephalosporium, Cladosporium, Monilia, Mucor, Penicillium, Rhizopus
Nashville, Tenn.	1940	Pennington[20]	Alternaria, Hormodendrum, Penicillium, Aspergillus, Mucor, Rhizopus
Missouri	1940	Hansel[15]	Alternaria, Hormodendrum, Helminthosporium
Detroit, Mich.	1941	Waldbott, Blair and Ackley[29]	Penicillium, Alternaria, Monilia, Aspergillus, Hormodendrum
Louisville, Ky.	1942	Vander Veer et al,[28]	Alternaria, Hormodendrum
Buffalo, N. Y.	1942	Cohen[7]	Hormodendrum, Alternaria, Penicillium, Mucor, Aspergillus
Chicago, Ill.	1942	Bernstein and Feinberg[3]	Alternaria, Hormodendrum
Central and Southwestern Parts of U. S.	1942	Morrow, Lowe and Prince[18]	Alternaria, Hormodendrum
San Diego, Cal.	1945	Harsh and Allen[16]	Hormodendrum, Alternaria, Penicillium, Macrosporium, Helminthosporium
San Antonio, Texas	1946	Bieberdorf[4]	Hormodendrum, Alternaria, Helminthosporium Spondylocadium, Fusarium, Aspergillus, Penicillium

those from outdoor air. The percentages of these molds in indoor air indicate that indoor air contains a mixture of the molds from outdoor air and of those from house dusts. Although *Phycomyces, Mucor,* and *Rhizopus,* the only Phycomycetes found, comprised 6.0 per cent, 1.7 per cent, and 3.2 per cent, respectively, of the molds in house dusts, these genera

were not encountered in either outdoor air or indoor air, except *Phycomyces,* which was found only to the extent of 0.7 per cent of the molds in indoor air. While *Macrosporium* and *Monotospora* were isolated only from out-

TABLE IV. MOLD GENERA REPORTED IN SURVEYS OF AIR-BORNE MOLDS

Mold genus	Number Investigators Reporting	Kentucky Survey
Alternaria	21	+
Penicillium	18	+
Aspergillus	17	+
Hormodendrum	17	+
Mucor	7	+
Helminthosporium	6	—
Cladosporium	5	—
Monilia	5	—
Rhizopus	5	+
Trichoderma	4	—
Macrosporium	3	+
Fusarium	2	—
Cephalosporium	1	+
Chaetomium	1	—
Monosporium	1	—
Oospora	1	+
Spondylocadium	1	—
Tilachlidium	1	+
Monotospora	0	+
Phycomyces	0	+
Stemphylium	0	+
Tetracoccosporium	0	+

TABLE V. DISTRIBUTION OF MOLDS IN OUTDOOR AIR, INDOOR AIR, AND HOUSE DUSTS
Condensed from Table I and Table II.

Molds	Outdoor Air %	Indoor Air %	House Dusts %
Fungi Imperfecti:			
Alternaria	17.8	10.6	1.5
Aspergillus	1.3	17.5	23.9
Cephalosporium	1.0	2.9	0.2
Hormodendrum	15.5	14.2	12.8
Macrosporium	0.7	0.0	0.0
Monotospora	1.6	0.0	0.0
Oospora	3.9	1.0	1.7
Penicillium	55.3	52.4	47.9
Stemphylium	0.7	0.0	0.0
Tetracoccosporium	0.0	0.0	0.4
Tilachlidium	2.2	0.7	0.7
Phycomycetes:			
Mucor	0.0	0.0	1.7
Phycomyces	0.0	0.7	6.0
Rhizopus	0.0	0.0	3.2
Totals	100.0	100.0	100.0

door air, and *Tetracoccosporium* was isolated only from house dusts, the percentage of each was too small to be of significance. *Penicillium, Hormodendrum,* and some of the molds that were found in small numbers were evenly distributed in outdoor air, indoor air, and house dusts.

Referring again to Tables I and II, it may be seen that certain species also were found to predominate in outdoor air, others in indoor air, and still others in house dusts. *Aspergillus luchuenis* was isolated almost entirely from house dusts, although the genus *Aspergillus* as a whole was

found almost as frequently in indoor air as in house dusts. Although the genus *Hormodendrum*, as a whole, appeared to be evenly distributed in the three sources, *Hormodendrum cladosporioides* was isolated almost entirely from house dusts, *Hormodendrum nigrescens* almost entirely from indoor air, and *Hormodendrum viride* almost entirely from outdoor air.

Perhaps the most significant finding of our survey is that certain molds occur predominantly in outdoor air and others in house dusts. It points to the possible importance of including house dust, as well as air, in surveys of mold distribution. This investigation is being continued.

SUMMARY AND CONCLUSIONS

A survey of mold distribution in outdoor air, indoor air and house dust in eastern Kentucky and in central and western Kentucky has been made.

Aside from *Penicillium and Phycomyces*, which were more prevalent in January, all the molds encountered in both months were more prevalent in March than in January. All the genera that were found in January were also found in March. In addition, eleven genera which were not found in January were found in March.

There was not much difference in the lists of mold genera encountered in the two regions of the state, except that *Monotospora* was encountered only in the central and western region while *Tetracoccosporium, Macrosporium* and *Stemphilium* were encountered only in the eastern region.

Penicillium was the most prevalent mold in both regions.

Of the genera reported in other parts of the country we failed to find *Monilia, Trichoderma, Helminthosporium, Cladosporium, Monosporium, Fusarium, Chaetomium* and *Spondylocadium*.

We found four genera, *Montospora, Stemphylium, Tetracoccosporium* and *Phycomyces*, that had not been previously reported.

Our finding that certain molds occur predominantly in outdoor air, and others in house dusts, points to the possible importance of including house dust, as well as air, in surveys of mold distribution.

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BACTERIOLOGICAL STUDIES OF MULTIPLE SCLEROSIS

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THE clinical diagnosis of the patients in this study was made by attending physicians and by consulting neurologists. The patients studied represented samplings of the disease from widely separated regions and widely different climates. The clinical history and physical examination gave no clue as to the probable cause of the disease, and its progressive course was similar regardless of place of residence, climate, occupation or nationality. The isolation, from infection atria in persons suffering from multiple sclerosis, of streptococci having elective affinity for the nervous system of animals and neurotropic cataphoretic velocity has been reported.[9,10] Evidence for the possible etiologic relationship of alpha streptococci isolated chiefly from nasopharynx, tonsils and teeth was sought by appropriate inoculation of animals, by agglutination and precipitation tests with the serums from persons afflicted, with antistreptococcic serum prepared in horses,[11] and with thermal antibody prepared *in vitro* from the streptococcus in NaCl solution suspensions by prolonged heating in the autoclave,[12] and with much less heat plus hydrogen peroxide.[14] In addition, presumptive tests were made for specific streptococcal antigen and antibody in skin or blood by intracutaneous injection of natural and thermal antibody and of streptococcal antigen, respectively.[15]

METHODS OF STUDY

Pus or other exudate was expressed and scooped from infected tonsils with a small-sized laryngeal mirror bent to an angle of 35°. Pus was aspirated from the depths of pyorrhea pockets with a capillary pipette. Pulpless teeth were drawn in a sterile manner and the apical end was immediately severed with a bone-cutting forceps. The nasopharynx was swabbed without touching the tongue, with aluminum wire cotton-wrapped swabs bent to a suitable angle to obtain material from up and behind the soft palate. The exudates from sinuses in persons having sinusitis, from cervix uteri in women suffering from endocervicitis, from the prostate in men having prostatitis and from the stool in special instances were obtained by suitable means.

The several materials thus obtained were suspended routinely in 2 ml. of 0.2 per cent gelatine in Locke's solution, for microscopic examination of Gram-saffranine stained films, for inoculation of animals and for cultures. The type and dosage for direct inoculation of animals and for cultures was modified as indicated by the kind and number of bacteria found in stained films. As a rule, two rabbits were inoculated intracerebrally far forward in the right frontal lobe, one with 0.1 ml., the other with 0.2 ml.

of the suspension in 2 ml. of gelatine-Locke's solution of the washings of nasopharyngeal swabbing, of washing of the apices of pulpless teeth, and of pus from pyorrhea pockets and tonsils. Cultures of these were made on blood agar and in dextrose brain broth. The latter afforded a gradient of oxygen tension and other conditions which were found essential for the growth and isolation of specific types of alpha streptococci.

The dextrose brain broth was either freshly prepared or was boiled to drive off oxygen and cooled immediately before being inoculated. Seven ml. of blood were drawn into vaccum tubes, allowed to clot, centrifuged, the serum poured off, the clot partially mascerated and planted into dextrose brain broth. Cultures in this medium were also made of the freshly drawn spinal fluid. The dextrose brain broth was prepared by adding pieces of fresh or frozen calf or young beef brain to tall columns, 9 to 10 cm. in test tubes of 0.2 per cent dextrose broth adjusted to pH 7.2, in a proportion of approximately one part by volume of brain substance to seven parts of the dextrose broth, before autoclaving at 17 pounds pressure for thirty minutes. All cultures were incubated at 33° to 35° C.

Early in these studies, animals were inoculated with the primary cultures from the one tube of dextrose brain broth which had been inoculated, provided stained films revealed a pure culture of the streptococcus. Blood agar plates were made at the same time to determine the purity and type of streptococcus. If other organisms had also grown in the dextrose brain broth, blood agar plates were made, and the subculture in dextrose brain broth from one or more colonies of the streptococcus which grew on the blood agar plate was injected into animals. More recently it was found that specifically virulent streptococci grew in far higher serial dilutions in dextrose brain broth than saprophytic variants and other bacteria often also present in the material studied. Serial dilutions were made in dextrose brain broth, at steps of 1-100 or 1-10,000 in four to six or more tubes, each containing 15 ml. of this medium. Serial dilutions at 1-100 were made by transferring and thoroughly mixing 0.15 ml. with the same 1 ml. pipette from tube to tube, and dilutions at 1-10,000 were made with a nichrome wire which was not sterilized after the first transfer and to which there adhered approximately 1.5 cubic millimeters of the culture. Pure cultures of the streptococcus for inoculation of animals and other studies were obtained from the end point of growth. Rabbits and guinea pigs were routinely inoculated intracerebrally with 0.1 or 0.2 ml. of a 1-200 or 1-10,000 dilution in NaCl solution, and mice with 0.03 ml. of the dextrose brain broth culture, and with these amounts, respectively, of 1-10,000 dilution of pure cultures in the autoclaved chick embryo medium.[13] Pure cultures of the streptococcus thus isolated in dextrose brain broth from the several materials from persons and from the brain or blood of inoculated animals were grown for one culture generation in varying amounts of 0.2 per cent dextrose broth. These cultures were centrifuged, the supernatant liquid was discarded, and the streptococci were placed in

dense suspensions of glycerol, two parts, and saturated NaCl solution, one part. These dense suspensions were made to contain the growth of from 150 to 500 ml. of the culture or approximately 300,000,000,000 to 1,000,000,000,000 organisms per ml. The suspensions containing the freshly isolated streptococci were kept in the refrigerator, and appropriate dilutions were made for precipitation and agglutination tests, for immunization of horses and for the preparation of vaccines and thermal antibodies. Agglutination tests were made at twofold dilutions of 1-20 to 1-160 or fivefold dilution of 1-10 to 1-1,250 of the serum from patients, and at fivefold dilutions of 1-20 to 1-2,500 of antistreptoccic serums and thermal antibody, in saline containing 0.2 per cent phenol, against suspensions in saline containing 0.2 per cent phenol and approximately 3,000,000,000 streptococci per ml. in the final dilution. The mixtures were incubated at from 48° to 50°C. for eighteen to twenty-four hours when readings were made. The degree of agglutination in each of the four dilutions was recorded according to the scale of 0 to 4 plus. A 4-plus agglutination in each dilution, or 16, would represent 100 per cent; a total of 6-plus, or 6/16 equalled 37.5 per cent of the total possible agglutination. The brain of animals and pieces of the medulla and spinal cord were fixed in 10 per cent formalin. Sections were stained with hematoxylin and eosin, by the Weigert method for myelin, and by a modified Gram-Weigert stain for bacteria, in which decolorization was carried to a fair blue instead of to the end point, and no counter stain was used.

RESULTS

Cultures from the blood and spinal fluid in dextrose brain broth proved negative except in a few instances in which alpha type of streptococci were isolated. Intracerebral injections of the spinal fluid in animals were without effect. Cultures from material obtained from nasapharynx, tonsils and infected teeth uniformly yielded streptococci of the viridans or alpha type, in great preponderance or in pure culture, and only occasionally small numbers of beta hemolytic streptococci. Staphylococci and micrococcus catarrhalis often grew in varying numbers on the primary blood agar plate, and H. influenzae almost never.

A careful search for associated infections was made in thirty-two cases. A history of repeated attacks of tonsillitis was obtained in seventeen, of an antecedent attack of influenza in thirteen. Clearly infected tonsils or tonsilar tags were found in nineteen, pyorrhea in twenty-four, and one or more pulpless teeth in twenty-eight.[17] In no instance did the disease begin following removal of foci of infection nor could relapses be traced to the removal. Since the methods and period of time covered in studies of multiple sclerosis were similar to those made of other diseases of the nervous system, and to afford a ready means of comparing the results obtained, a summary of the results in these and in normal controls is included.

The mortality, incidence of symptoms, and isolations of the streptococcus

TABLE I. MORTALITY AND SYMPTOMS IN RABBITS FOLLOWING INTRACEREBRAL INOCULATION OF STREPTOCOCCI ISOLATED IN STUDIES OF MULTIPLE SCLEROSIS AND OTHER DISEASES OF THE NERVOUS SYSTEM AND ISOLATION OF STREPTOCOCCI FROM THE BRAIN OF INOCULATED ANIMALS

Groups and Inocula. Streptococci from Nasopharynx, Tonsils, Sinuses or Infected Teeth		Cases	Rabbits		Incidence of Symptoms (per cent)						Cultures from	
			Inoculated	Per Cent That Died	Hyperirritability	Tremors	Spasms	Convulsions	Ataxia	Nystagmus	Paralysis	Brain	Per Cent Yielding Streptococci
Multiple Sclerosis	Suspensions in NaCl solution	18	46	65	46	**72**	24	1	**74**	**26**	**50**	40	62
	Dextrose brain broth cultures diluted 1-200 to 1-10,000 — As isolated	24	42	52	29	**74**	21	0	**52**	**35**	**42**	34	65
	Dextrose brain broth cultures diluted 1-200 to 1-10,000 — After animal passage	19	34	62	35	**65**	24	1	**74**	**22**	**50**	30	60
	Total	61	122	60	36	**70***	23	2	**66**	**29**	**49**	104	63
Spasmodic Torticolis		8	70	69	6	**40**	21	0	**59****	11	22	58	67
Persistent hiccup		28	176	70	23	**40**	**66*****	0	**59**	19	22	130	89
Encephalitis		50	60	60	25	**58**	**55**	15	**40**	10	13	41	80
Poliomyelitis		68	145	46	26	33	35	2	23	2	**70**	62	91
Idiopathetic Epilepsy		46	106	74	25	**75**	**75**	**34**	13	5	16	72	93
Schizophrenia		45	77	**87**	**87**	**79**	21	3	10	0	9	54	83
Normal Controls		77	106	**23**	2	4	2	0	16	**7**	8	97	**25**

*Usually of severe "intension" type.
**Accompanied by tic-like and spasmodic movements of the head.
***Especially of the diaphragm.

from the brain of rabbits that were inoculated directly with saline suspensions or with cultures of the streptococcus on isolation and after animal-passage, from altogether sixty-one persons suffering from multiple sclerosis, and in contrast the result in rabbits similarly inoculated with streptococci from spasmodic torticolis, persistent epidemic hiccup, encephalitis, poliomyelitis, epilepsy and schizophrenia and normal controls, are summarized in Table I. The mortality and isolations of streptococci from brain of inoculated rabbits and the incidence of symptoms referable to the nervous system were consistently much higher following inoculations of streptococci from persons suffering from multiple sclerosis and the other diseases of the nervous system than in those receiving the streptococcus from normal controls. The incidence and type of symptoms referable to the nervous system in the three groups of rabbits receiving streptococci isolated in studies of multiple sclerosis were strikingly similar to those at hand in persons suffering from this disease. The mortality and incidence of isolations of the streptococcus from brain of mice and guinea pigs receiving the streptococcus from multiple sclerosis were similar to those obtained in rabbits. Lesions of lungs in mice inoculated intraperitoneally were abnormally high, occurring in ten of eighteen mice so inoculated. Of 117 mice inoculated intracerebrally with forty strains of the streptococcus, seventy-three (62 per cent) died. Severe tremors were observed in forty-five, spasms in twenty-eight, ataxia in ten, paralysis in twenty-three and incontinence of urine in six. The streptococcus was isolated from the brain in thirty-four of the thirty-eight cultured. Of sixty-eight guinea pigs inoculated intracerebrally with twenty-six strains, thirty-six (53 per cent) died. Severe tremors developed in thirty-one, spasms in eighteen, ataxia in ten, paralysis in twenty-five, incontinence of urine in four and salivation with wet fur under chin in five. The streptococcus was isolated from the brain in twenty-seven of the twenty-nine cultured.

The incidence and type of symptoms in animals receiving the streptococcus isolated in studies of the other diseases of the nervous system were likewise similar in important respects to those more or less characteristic of the diseases in question. The statistical evidence of specificity, though often striking, does not adequately represent the results. Blurred vision or blindness, hyperactive reflexes and incontinence of urine, which developed not uncommonly in animals following inoculation of streptococci isolated in studies of multiple sclerosis, were not obtained or were obtained less often following inoculation of streptococci isolated in studies of the other diseases, and never following inoculation of the streptococcus from normal controls. Paralysis in the multiple sclerosis group of animals was relatively mild, usually spastic in type and was often associated with localized spasms. Ataxia, accompanied by tic-like and spasmodic movements of the head, was the characteristic picture in animals following inoculation of the streptococcus isolated in studies of spasmodic torticolis. Ataxia spasms of the diaphragm and abdominal muscles, sometimes associated with audi-

ble hiccup and hemorrhages in the diaphragm, characterized the findings in animals inoculated with the streptococcus isolated in studies of epidemic and postoperative hiccup. A wide range of symptoms developed in rabbits receiving the streptococcus isolated in studies of encephalitis, which corresponded to the wide range of symptoms at hand in the patients from whom the streptococcus inoculated was obtained. Muscular spasms and lethargy occurred in high incidence in animals receiving the streptococcus isolated, respectively, from persons having myoclonic and lethargic types of encephalitis. Flaccid paralysis with diminution or loss of knee jerks occurred in highest incidence in the poliomyelitis group of animals, and tremors, spasms, and ataxia were slight or absent. Moreover, nystagmus and incontinence of urine almost never occurred. The presence of specific types of streptococci in epidemic encephalitis and poliomyelitis is obviously not to be considered as the sole cause of these diseases independently of the viruses. Severe tremors and spasms, often associated with generalized convulsions resembling grand mal, occurred in highest incidence in the group of animals receiving the streptococcus from persons suffering from idiopathic epilepsy.[16] Extreme hyperirritability and tremors occurred in highest incidence in the group of animals receiving the streptococcus isolated in studies of schizophrenia. Catatonic states and strange changes in behavior often also developed in these, and virtually never occurred in the other groups of animals.[16]

Sterile filtrates of NaCl solution suspensions of material obtained directly from nasopharynx, tonsils and teeth, and of the dextrose brain broth cultures from persons having multiple sclerosis, when injected intracerebrally, caused transient tremors, in-co-ordination, congestion of eyes, and other mild symptoms soon after injection, followed by recovery. Late symptoms or deaths, indicating the possible presence of a virus, did not occur.

Streptococci isolated from the cervix uteri, from prostate and from the stool were without neurotropic virulence. The invasiveness or general virulence of the streptococcus isolated in studies of multiple sclerosis, in accord with the nature of the disease, was found to be of a low order. Inoculated animals did not die of a streptococcemia. Cultures were made of the blood of ninety-two rabbits that died after intracerebral inoculation of the streptococcus. The cultures remained sterile in seventy-three, and in only nineteen was the streptococcus obtained. Of the nineteen rabbits, the streptococcus was isolated in nine of twelve that died in twenty-four hours after inoculation; in six of nineteen that died on the second day; in three of thirteen that died on the third day; in one of eight that died on the fourth day, and in none of forty that died on the fifth to the sixtieth day.

As shown in Table I, cultures were made from the brain in 104 of the 122 rabbits that had been inoculated with material containing the streptococcus. Sixty-five (63 per cent) yielded the streptococcus. While the cultures in thirty-nine proved sterile, most of the thirty-nine died late from

the effects of the inoculation, and a few were anesthetized while having active symptoms. Cultures from the blood of all of these remained sterile, and the streptococcus was not demonstrable in the lesions. The late symptoms and deaths were clearly due to causes other than an overwhelming infection. The probable presence of a streptococcal neurotoxin having predilection for vital nerve centers, or to which the vital centers had become allergic, was considered. Accordingly, emulsions of the brain and filtrates of emulsions were made from rabbits that died late, and whose blood and brain proved sterile, and from normal rabbits. These were inoculated intracerebrally into normal rabbits. All of six rabbits receiving emulsions and four receiving filtrates died—three on the day after inoculation, two in three days, two in four days, one in seven, and two in fourteen days. The material inoculated and cultures from the brain of all that died proved sterile. None of these rabbits developed symptoms suggestive of multiple sclerosis. The emulsions of the brain and filtrates of emulsions from normal rabbits similarly inoculated proved innocuous.

ILLUSTRATIVE EXPERIMENTS IN ANIMALS AND PROTOCOLS

A mixture of equal parts of the cultures of the streptococcus isolated from the nasopharynx of sixteen persons suffering from multiple sclerosis, and grown separately in chick embryo medium for from seven to forty-two days, was made, and a 1-10,000 dilution was inoculated intracerebrally in eight rabbits, twelve guinea pigs and one monkey. Intension tremors developed in seven of the eight rabbits and in eight of the twelve guinea pigs, ataxia in six and five, respectively, exaggerated knee jerks in eight and seven, nystagmus in six and two, ataxia in six and two, localized paralysis in seven and eight, spasms of muscles in five and six, incontinence of urine in four and three, and drooling of saliva in two and four. Blurred vision developed in three, and blindness in two, of the eight rabbits. Seven of the rabbits and seven of the guinea pigs died in from two to twelve days following inoculation. The rest were anesthetized. The streptococcus was isolated from the brain in dextrose brain broth in all of the twelve guinea pigs and in the rabbits that died within six days, and in only one of the rest. The details of experiments and results obtained in this series of rabbits, guinea pigs and the monkey, and in other rabbits, are depicted in Protocols 1, 2, 3, and 4.

Protocol 1.—A white rabbit weighing 1,800 grams was injected intracerebrally on June 11, 1943, with 0.1 ml. of sterile chick embryo medium to lower the inherently high resistance of the brain to infection, and 2 ml. of the undiluted culture from nasopharynx was injected into the tongue. The animal was well June 12. On June 13, moderate tremors of masseters and muscles of the neck and tremors of extremities on exertion were noted. On June 14, weakness of the left fore extremity, severe tremors and twitchings of the muscles of the neck, exaggerated reflexes and ataxia had developed. The paralysis and tremors were worse on June 15, and the animal was found dead on June 16. Moderate hemorrhagic edema of lungs and congestion of

TABLE II. AGGLUTINATIVE TITER OF THE SERUM OF PERSONS SUFFERING FROM MULTIPLE SCLEROSIS, MIGRAINE, SCHIZOPHRENIA AND ARTHRITIS FOR STREPTOCOCCI ISOLATED IN STUDIES OF THE RESPECTIVE DISEASES

Serums from Persons Suffering from:	Number of Serums	Average Cutaneous Reaction Indicating Antibody	Percentage of Agglutination by Serum of Patients at Twofold Dilutions of 1-20 to 1-160 of: Streptococci isolated in studies of: Multiple sclerosis, stages: Active					Quiescent		Migraine	Schizophrenia	Arthritis
			8463	3248	2405	3706	3749	3027	3238	3709	2839	3761
Multiple Sclerosis	6	High (10.67 sq. cm.)	**32**	**59**	**35**	**72**	**69**	0	0	19	12	4
	7	Moderate (4.91 sq. cm.)	**29**	**55**	**28**	**76**	**58**	0	0	13	2	1
	7	Low (1.65 sq. cm.)	**24**	**49**	**21**	**58**	**44**	0	0	18	9	0
Migraine	7	6.28 sq. cm.	4	22	13	32	27	0	0	**51**	13	4
Schizophrenia	6	4.91 sq. cm.	0	17	8	33	19	0	0	17	**30**	0
Arthritis	3	7.85 sq. cm.	2	19	5	33	20	0	0	4	4	**35**

the brain were found. Cultures in dextrose brain broth from the brain and blood yielded a pure culture of the streptococcus.

Protocol 2.—A medium-sized white rabbit was inoculated intracerebrally on June 1, 1943, with 0.1 ml. of a 1-10,000 dilution in 0.2 per cent dextrose brain agar of a serial dilution culture of the streptococcus which grew in dextrose brain broth at 10^{-8} dilution of the NaCl solution washings of the nasopharyngeal swabbing. On June 2 the animal seemed well when quiet in its cage, but on exertion, tremors of extremities developed. On June 3, extreme intension tremors, ataxia, exaggerated knee reflexes and weakness of adductors of fore extremities were noted. From June 3 to 8, the animal remained about the same. On June 9 it seemed well when quiet in cage, but on exertion, severe tremors, ataxia, blurred vision, horizontal nystagmus and tilting of head to the right were noted. On June 10 it was about the same. On June 11 and 12, the symptoms were worse, and the animal was found dead on June 13. There was no mark at the point of intracerebral injection. The meninges were normal. The brain was moderately congested. The optic nerves were congested and edematous. There were no lesions of the viscera. Dextros brain broth cultures from the brain yielded a pure culture of the streptococcus.

Protocol 3.—A guinea pig weighing 350 grams was inoculated intracerebrally on June 11, 1943, with 0.01 ml. of a 1-10,000 dilution of the chick embryo cultures of *the streptococcus.* On June 12 and 13, there were no apparent symptoms. On June 14 severe tremors on exertion and moderate spastic paralysis of hind extremities were noted. On June 16 spastic gait, ataxia, severe intension tremors, nystagmus and wetting of the fur under the chin were present. On June 17 the symptoms were about the same. On June 19 intension tremors were extreme, often bordering on generalized spasms, associated with severe ataxia and spastic weakness of hind extremities. It was anesthetized to death. Fur under the chin was wet due to drooling of saliva. Aside from moderate congestion of the brain, no lesions were found. Dextrose brain broth cultures from the brain yielded a pure culture of the streptococcus.

Protocol 4.—A medium-sized rhesus monkey was inoculated intracerebrally on June 1, 1943, with 2 ml. of a 1-10,000 dilution in .2 per cent dextrose brain agar of the primary dextrose brain broth culture of the streptococcus from the nasopharyngeal swabbing of a person in the active stage of multiple sclerosis. The monkey was apparently well on June 2. On June 3 it seemed well when undisturbed in its cage, but when it jumped from its cage, undoubted weakness of hind extremities was noted. On June 4, severe tremors on exertion, horizontal nystagmus and incontinence of urine had developed. The temperature was normal. These symptoms disappeared, and on June 11 it was inoculated intracerebrally with 1 ml. of a 1-10,000 dilution of the mixtures of the chick embryo cultures of the streptococci from the sixteen persons having active symptoms of multiple sclerosis, and intralingually with 2 ml. of the undiluted mixture of cultures. On June 12 at 9:00 a.m., the animal refused to leave its cage, and when made to do so, severe tremors and undoubted weakness of hind extremities and incontinence of urine became manifest, and exaggerated knee jerks were elicited. On June 13 it sat quietly in its cage, apparently blind. On exertion, severe tremors, bordering on mild generalized spasms, ataxia, and spastic weakness of extremities were noted. It bumped into the walls of its cage as it moved aimlessly about. The pupils were widely dilated and did not respond to light. Severe and continuous horizontal nystagmus had developed. On June 14 it was found dead. Necropsy revealed congestion of the brain, infiltration and edema surrounding the optic nerve and chiasm, and also of spinal nerves and the anterior aspect of the medulla. A small cyst was found at the point of injection in the

TABLE III. AGGLUTINATION OF STREPTOCOCCI ISOLATED IN STUDIES OF MULTIPLE SCLEROSIS AND OTHER DISEASES BY THE SERUMS OF PERSONS HAVING MULTIPLE SCLEROSIS AND THE SERUMS FROM PERSONS CONVALESCING FROM RESPIRATORY INFECTIONS

Pools of Streptococci Isolated in Studies of:	Number of Strains in Pools	Percentage of Total Possible Agglutination by the Serums at Fivefold Dilutions of: 1-10 to 1-1250 of persons: Suffering from: Multiple Sclerosis. Average for Serums from 10 cases	Convalescent from: Respiratory Infections. Average for Serums from 40 cases
Multiple Sclerosis	10	**66**	31
	7	**72**	33
Encephalitis		33	20
Poliomyelitis		21	5
Respiratory Infection	Many	12	**53**
Arthritis		13	9
Well Controls		19	13

TABLE IV. AGGLUTINATIVE TITER OF ANTISTREPTOCOCCIC SERUMS FOR CLOSELY RELATED, HOMOLOGOUS AND DISTANTLY RELATED STREPTOCOCCI

Source of Streptococci	Strains or Cases	Cultures	Percentage Incidence of Maximal and Indeterminate Agglutinations at Fivefold Dilutions of 1-20 to 1-2500 by Antiserums Prepared with Streptococcus Isolated in Studies of: Encephalitis	Poliomyelitis	Influenza	Arthritis	Epilepsy	Schizophrenia	Indeterminate
Multiple Sclerosis	19	98	**64**	23	5	0	—	—	8
Encephalitis	10	12	**58**	0	0	0	17	25	0
Epilepsy	10	12	8	0	0	0	**75**	**517**	0
Schizophrenia	23	45	13	0	0	0	31	**7**	0
Arthritis	10	30	7	0	3	**70**	10	0	10
Normal Controls	71	71	15	4	17	7	12	7	38

right frontal lobe. The viscera were normal. Dextrose brain broth cultures of pipettings of cerebrospinal fluid-admixed with brain substance revealed a pure culture of the streptococcus.

RESULTS OF AGGLUTINATION AND PRECIPITATION TESTS

The results of agglutination tests made with the serums and streptococci from persons having multiple sclerosis, in contrast to those obtained in control studies, are summarized in Table II. It will be seen that the streptococci isolated in studies of multiple sclerosis, migraine, schizophrenia and arthritis were agglutinated in highest titer by the respective homologous serums. Moreover, the agglutinative titer of the serums and the antibody titer in skin or blood, as determined by the cutaneous tests, ran closely parallel. This was especially true in multiple sclerosis. The streptococci isolated during the quiescent stage of multiple sclerosis were not agglutinated by any of the serums.

The agglutinative titers of serums from persons having active multiple sclerosis, and, in contrast, of serums from persons convalescing from respiratory infections, for streptococci isolated in studies of persons having

TABLE V. AGGLUTINATION OF STREPTOCOCCI BY THERMAL ANTIBODY PREPARED FROM STREPTOCOCCI ISOLATED IN STUDIES OF MULTIPLE SCLEROSIS AND OTHER DISEASES

Thermal Antibody Prepared from Streptococci Isolated in Studies of:	Pools of Strep-to-cocci	Percentage of Total Possible Agglutination of Respective Streptococci at Fivefold Dilutions of from 1-20 to 1-2500 of Thermal Antibody Prepared from Streptococci Isolated in Studies of:							
		Multiple Sclerosis		Respir-atory Infec-tion	Schizo-phrenia	Mi-graine	Arthri-tis	Controls	
		8463	3749	3738	2839	3750	3961	Pneu-mococci Types I, II, III	Staph-ylo coccus
Multiple Sclerosis	8463	**63**	**81**	56	56	50	56	38	31
	3749	**63**	**88**	63	63	69	50	19	31
Respiratory Infection	3738	50	63	**88**	69	69	50	19	19
Schizophrenia	2839	38	63	56	**81**	63	44	25	13
Migraine	3750	31	56	69	69	**88**	56	19	13
Arthritis	3961	13	44	56	50	44	**69**	19	19
Controls—Type Pneumococci I, II, III	3689	0	25	44	44	50	38	**69**	25
Staphylococci	8406	0	25	19	31	25	25	19	**44**
NaCl Solution		6	19	25	19	25	25	19	13

TABLE VI. PRECIPITATION AT THE INTERFACE BETWEEN THE SERUMS AND WASHINGS OF NASOPHARYNGEAL SWABBINGS OF PERSONS HAVING MULTIPLE SCLEROSIS AND ANTISERUMS PREPARED WITH STREPTOCOCCI ISOLATED IN STUDIES OF ENCEPHALITIS, POLIOMYELITIS AND RESPIRATORY INFECTIONS

Materials Used as Antigen		Cases	Percentage Incidence of Precipitation at the Interface with:					
			Antiserums Prepared in Horses with Streptococci Isolated in Studies of:				Anti-pneumo-coccic Serums I, II, III	Normal Horse Serum
			Enceph-alitis	Polio-myelitis	Respir-atory Infec-tion	Arthri-tis		
Serums from Cases		5	**80**	**60**	20	0	0	0
		16	**50**	**62**	**62**	0	7	0
		11	**55**	**36**	**55**	18	0	0
NaCl Solution Washings from Nasopharyngeal Swabbings	Undiluted	17	**76**	**82**	**88**	0	0	0
	Diluted 1-10		**41**	**41**	**29**	0	0	0
	Undiluted	11	**100**	**100**	**73**	27	18	0

these and other diseases, are summarized in Table III. A high degree of respective specificity is shown.

The results of a long series of agglutinative tests with antiserums prepared in horses with streptococci isolated in studies of different diseases of the nervous system, of influenza and of arthritis, and the homologous, closely and distantly related streptococci, are summarized in Table IV. Agglutinative titers for homologous and closely related strains were consistently much higher than for more distantly related strains. Evidence indicating antigenic and other differences in alpha streptococci isolated in studies of multiple sclerosis, and of those isolated in studies of other dis-

TABLE VII. ERYTHEMATOUS REACTIONS FOLLOWING INTRADERMAL INJECTION OF "NATURAL" AND THERMAL ANTIBODY IN PERSONS HAVING MULTIPLE SCLEROSIS IN RELATION TO HISTAMINE INJECTIONS

Groups	Reactions to Intradermal Injection of:											
	Natural Antibody						Thermal Antibody					
	Prepared from Streptococci Isolated in Studies of:											
	Persons Tested	Polio-myelitis	Encepha-litis	Arthritis	Respir-atory Infection	Pneumo-coccal Types I, II, III	Persons Tested	Polio-myelitis	Encepha-litis	Arthritis	Multiple Sclerosis	Well Persons
Multiple Sclerosis: 24 hours after daily Histamine Injections	10	**5.96**	**9.80**	2.60	1.33	—	14	5.16	7.24	2.88	**13.23**	1.08
Multiple Sclerosis: Histamine Injections	13	**6.11**	**8.38**	2.12	—	1.42	12	2.96	6.24	2.88	**13.57**	
Multiple Sclerosis: No Histamine Injections	9	**7.64**	**11.48**	2.42			15	1.78	6.61	2.82	**18.46**	0.93
Well Persons Remote from Epidemics	Many	1.27	0.79	1.48	2.23	—	Many	1.80	0.79	1.54	0.83	0.89
Encephalitis	Many	3.27	**6.88**	1.80	3.06	—	Many		**9.23**	2.21		
Poliomyelitis	Many	**8.97**	3.30	2.41	3.21		Many	**14.21**	4.21	2.45		3.09
Persistent Hiccup	Many	4.10	**7.38**	3.12	5.12		Few		**12.32**	1.76		
Arthritis	87	1.50	2.60	**8.12**			19		3.47	**9.63**		

eases, is strikingly shown in Table V. Comparable suspensions in NaCl solution of each of the different groups of strains, when autoclaved with hydrogen peroxide, yielded agglutinins in highest titer for the respective homologous strains.[14]

Results of precipitation reactions at the interface between the serums of horses that had been immunized with streptococci from encephalitis, poliomyelitis and respiratory infections closely related to streptococci from multiple sclerosis, and the serums and NaCl solution extracts of nasopharyngeal swabbings from persons having multiple sclerosis, are summarized in Table VI. A much higher incidence of precipitation occurred with the antiserums from encephalitis, poliomyelitis and respiratory infections than with antiserums prepared with the streptococci from arthritis, and than with anti-pneumococcic and normal horse serum.

The effects of intravenous injections of histamine on the specific streptococcal antigen content in skin or blood, determined by the intradermal injection of "natural" and artificial or thermal streptococcal antibody[12] in persons having multiple sclerosis, are summarized in Table VII. A significant diminution in antigen occurred, as measured by the intradermal injection of natural antibody prepared in horses with streptococci isolated in studies of encephalitis and poliomyelitis, and a striking specific drop occurred as measured with thermal antibody prepared *in vitro* from streptococci isolated in studies of multiple sclerosis.

The effects of intravenous injections of histamine on the cutaneous reactions to the specific thermal antibody and antigen in thirteen persons having multiple sclerosis are summarized in Table VIII. The reactions to antibody, indicating antigen, were uniformly far greater, and to antigen, indicating antibody in skin or blood, were uniformly far less, in the two persons before treatment with histamine and the seven other persons not receiving histamine (not included in the table) than the reactions indicating antigen and antibody, respectively, one-half to two hours after daily intravenous histamine injections. Moreover, reactions indicating antigen were significantly less in twelve of the thirteen persons receiving histamine, and reactions indicating antibody greater in eight, one-half to two hours after histamine, than the reactions twenty-four hours after histamine injections. The diminution in antigen and increase in antibody was by far the greatest after the first histamine treatment.

The effects on the cutaneous reactions to natural antibody, prepared with closely related streptococci from encephalitis and poliomyelitis, of treatment of persons having multiple sclerosis with histamine alone, and of treatment with histamine and specific thermal antibody, are summarized in Table IX. It will be seen that there was a far greater reduction in reactions indicating antigen following the combined treatment, than with histamine alone. This is in accord with the results obtained in a number of persons having multiple sclerosis treated with vaccine and thermal antibody prepared from streptococci isolated in studies of multiple

TABLE VIII. THE EFFECT OF HISTAMINE INJECTIONS IN PERSONS HAVING MULTIPLE SCLEROSIS ON THE SPECIFIC STREPTOCOCCAL ANTIGEN AND ANTIBODY TITER IN SKIN OR BLOOD AS DETERMINED BY THE REACTION FOLLOWING INTRACUTANEOUS INJECTION RESPECTIVELY OF THERMAL ANTIBODY AND OF ANTIGEN

No.	Age	Sex	Number of Histamine Treatments		Clinical Results	Cutaneous Reactions (sq. cm.) Indicating Streptococcal Antigen and Antibody Respectively in Skin or Blood Characteristic of:					
						Multiple Sclerosis		Arthritis	Multiple Sclerosis		Arthritis
			Previous Series	Present Series		Antigen	Antibody	Antigen	Antigen	Antibody	Antigen
						24 Hours after Previous Treatment			½ to 2 Hours after Histamine Treatment		
3710	35	M	0	1	?	19.64*	1.77	4.91	**3.14**	**12.57**	3.14
3711	21	F	0	1	?	19.64*	1.77	3.14	**7.07**	**12.57**	1.77
3700	19	M	0	26	Improved	9.62	3.14	0	**7.07**	**4.91**	0
3701	33	M	0	22	Improved	9.62	12.57	0	**3.14**	4.91	0
3705	29	F	0	36	Improved	9.62	7.07	0	**7.07**	**9.62**	0
3717	46	F	0	40	Improved	4.91	9.62	4.91	**3.14**	**12.57**	0
3713	38	F	0	62	Improved	3.14	7.07	3.14	4.91	4.91	0
3704	27	F	Many	59	Improved	12.57	7.07	0	**3.14**	**9.62**	4.91
3703	36	M	200	10	Markedly Improved	7.07	12.57	0	**3.14**	4.91	4.91
3712	48	F	Many	18	Markedly Improved	3.14	4.91	0	**1.77**	**7.07**	0
3714	52	F	382	45	Disease Quiescent	1.77	12.57	0	**0**	12.57	0
3716	51	F	39	46	Improved	4.91	9.62	4.91	**3.14**	**12.57**	0
3702	32	M	200	?	Improved	7.07	12.57	0	**3.14**	4.91	0
Total average						8.67	7.10	0.91	4.45	8.75	1.06

TABLE IX. THE EFFECT ON CUTANEOUS REACTIONS IN PERSONS HAVING MULTIPLE SCLEROSIS OF TREATMENT WITH HISTAMINE ALONE AND TREATMENT WITH HISTAMINE AND SPECIFIC THERMAL ANTIBODY

Groups		Cases	Erythematous Reactions to Intradermal Injection of Natural Antibody Prepared in Horses with Streptococci Isolated in Studies of:							
			Chronic Encephalitis		Acute Poliomyelitis		Arthritis		Pneumonia	
			Sq. cm.	Reactions 5 sq. cm. or more. Per Cent	Sq. cm.	Reactions 5 sq. cm. or more. Per Cent	Sq. cm.	Reactions 5 sq. cm. or more. Per Cent	Sq. cm.	Reactions 5 sq. cm. or more. Per Cent
Multiple Sclerosis	Before Treatment	9	10.34	78	5.84	56	2.54	11	0	0
	After from 8 to 45 Daily Treatments with Histamine	9	7.44	78	4.54	47	1.71	0	1.48	0
	After from 1 to 47 Daily Treatments with Histamine and from 1 to 10 Injections of Thermal Antibody*	7	2.11	0	2.21	0	0.81	0	0	0
Arthritis, untreated controls		8	1.45	0	1.18	0	4.74	63	1.06	0

*Thermal antibody was injected subcutaneously every other or every third day. Each injection consisted of 1 ml. of a 1-10 dilution of the supernatant of NaCl solution suspension of 20,000,000,000 streptococci per ml. isolated in studies of multiple sclerosis after autoclaving for 96 hours.

sclerosis. These results were similar to those obtained in a man of middle age having advanced multiple sclerosis. The cutaneous reaction to antibody on January 3, 1947, before treatment, was 19.64 sq. cm., and to antigen, 0. On February 24 these reactions were 15.90 and 12.57, respectively; on May 21, 7.07 and 4.91, and on Nov. 11, 3.14 and 4.91. Coincident with the striking reduction of antigen and increase of antibody, the symptoms indicating activity disappeared.

THE GROSS AND MICROSCOPIC LESIONS

Abscess formation in the brain at the site of injection of material containing the streptococcus and diffuse suppurative meningitis almost never occurred. Diffuse congestion of the brain, edema, and leukocytic infiltration over the anterior surface of the pons and medulla were common, especially in rabbits that died in from two to four days following inoculation of washings of nasopharyngeal swabbings and suspensions of pus from tonsils and pyorrhea pockets. This was less common following inoculation of highly diluted pure cultures of the streptococci. Severe congestion of the mucous membrane of the trachea, with or without hemorrhagic edema of the lungs, was found commonly in rabbits that succumbed soon after inoculation. The bladder was often greatly distended with urine in animals in which severe paralysis had developed.

The microscopic lesions were most numerous in the white matter of the cerebrum, pons, peduncles of cerebellum and the posterior and lateral col-

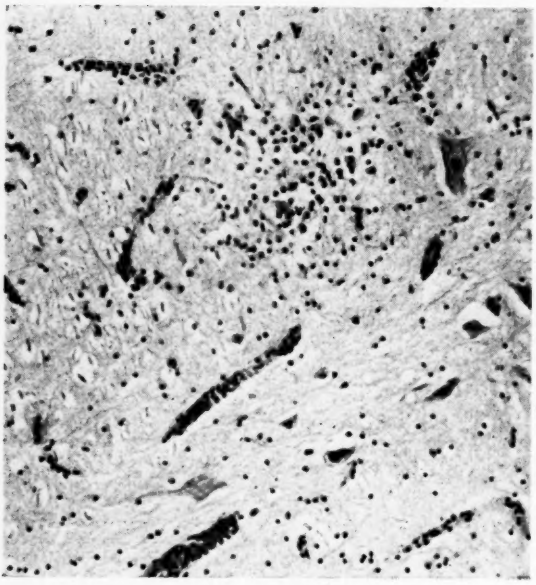

Fig. 1. Area of degeneration and round cell infiltration surrounded by partially occluded blood vessels, due to endovascular and perivascular infiltration by round cells in the lateral column of the spinal cord of a rabbit, seven days after intracerebral inoculation of the streptococcus. H. and E. stain × 175.

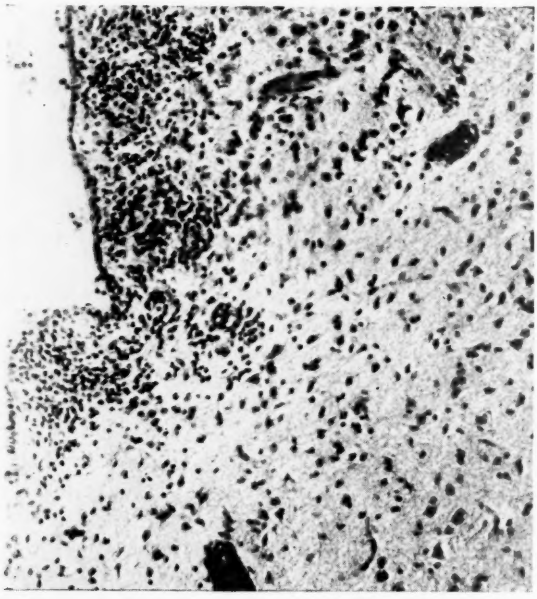

Fig. 2. Perivascular and diffuse round cell infiltration in the wall of the lateral ventricle in the brain of a rabbit, seven days following intracerebral inoculation of the streptococcus. H. and E. stain × 175.

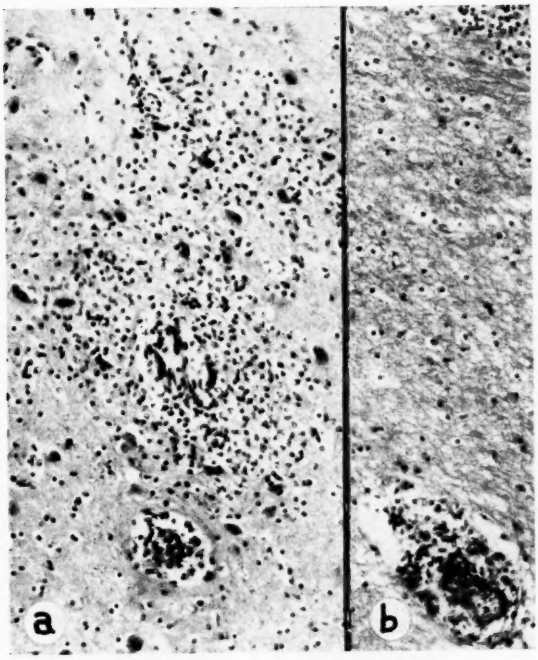

Fig. 3. (a) Endovascular, perivascular and diffuse round cell infiltration, degeneration and edema in the midbrain, and (b) perivascular infiltration, edema and degeneration in the cerebellum of a monkey, thirteen days following the first and two days following the second intracerebral inoculation of the streptococcus (Protocol 4). H. and E. stain × 175.

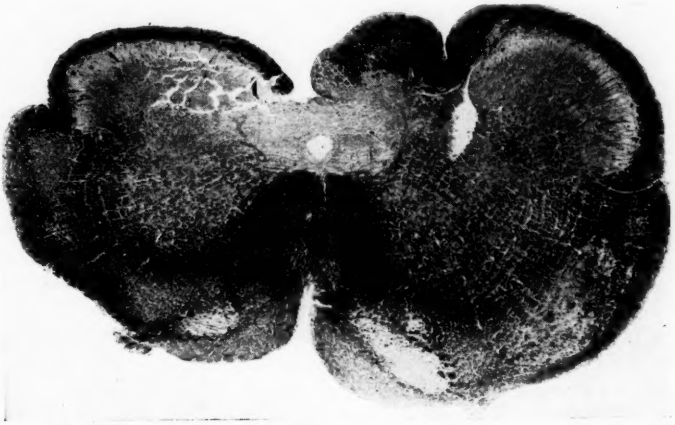

Fig. 4. Medulla of the rabbit, referred to in Protocol 2, twelve days following intracerebral inoculation of a 1-10,000 dilution of dextrose brain broth culture of the streptococcus. Note the unstained extensive patchy disseminated areas of demyelinization especially posteriorly. Weigert myelin stain × 12.

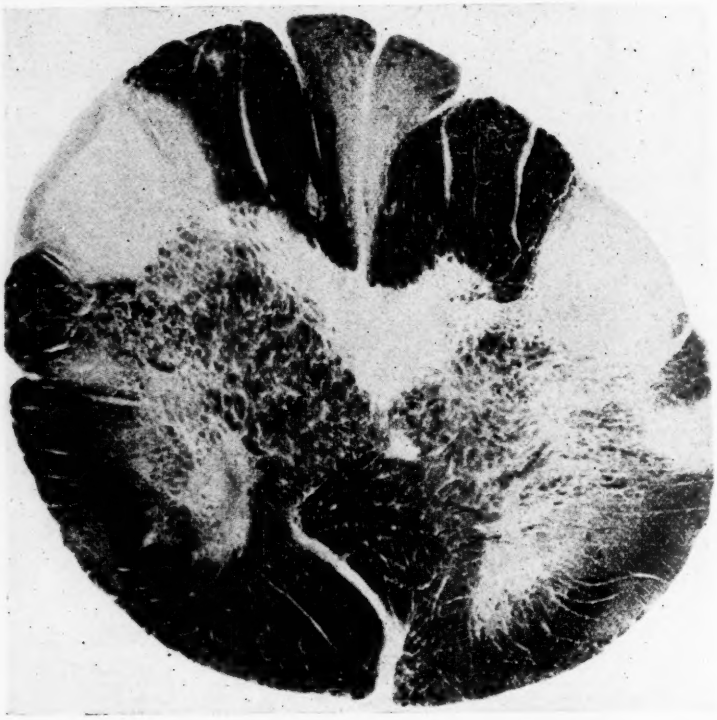

Fig. 5. "Disseminated sclerosis—medulla. Several areas of demyelinisation are present in the section. These are unstained, well-defined and variable in size and shape."[7] The photomicrograph is of a person that died of multiple sclerosis. Weigert-Pal myelin stain × 9.

umns of the spinal cord. Hemorrhages, edema, polymorphonuclear leukocytic infiltration, and degeneration, especially surrounding blood vessels, characterized the microscopic picture in animals that succumbed soon after inoculation. Degeneration and infiltration by lymphocytes and plasma cells predominated in the lesions of animals that died or were anesthetized long after inoculation. The lesions were often related to blood vessels which were partially or completely occluded by thrombi, or more often, by endovascular and perivascular proliferation of cells resembling lymphocytes, endothelial, and plasma cells (Figs. 1, 2 and 3). Occlusion of blood vessels by fibrinous clots of fibrin were not found.[6] Hemorrhage and edema were found in the wall and immediately surrounding fair-sized blood vessels in the pia and white matter of the medulla and in the posterior and lateral columns of the spinal cord. Regardless of these important lesions, the most striking parallelism between the experimentally produced and natural occurring lesions was the demyelinization, as shown by the Weigert and Weigert-Pal special stains for myelin[7] (Figs. 4 and 5). The optic nerves

Fig. 6. Edema and interstitial round cell infiltration of the optic nerve of the monkey in which blindness developed (Protocol 4). Note in addition the absence of lesions within the eye and the great swelling of the optic nerve immediately outside of the inelastic sclera of the eyeball. H. and E. stain × 25.

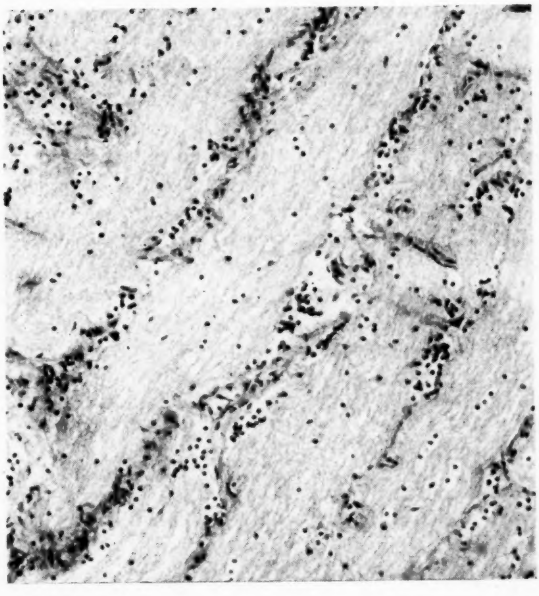

Fig. 7. Interstitial edema and round cell infiltration of the optic nerve shown in Fig. 6. H. and E. stain × 175.

of the monkey that became blind were edematous and swollen (Fig. 6). In some instances, the posterior roots of the spinal nerves were found edematous and infiltrated, but in no instance were lesions found in the inter-

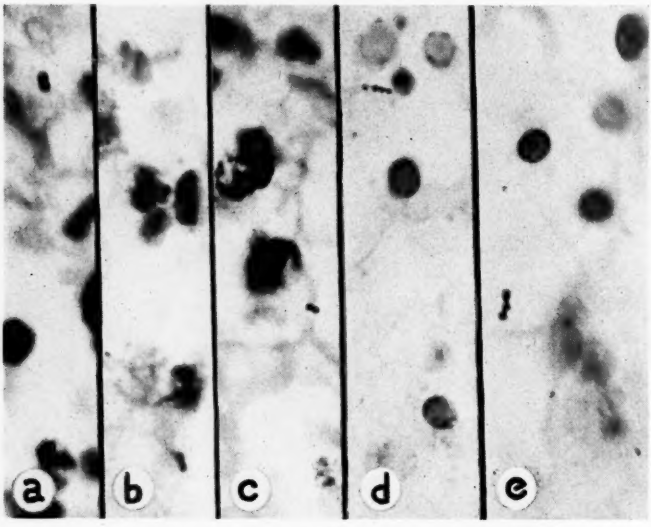

Fig. 8. Diplococci or streptococci in perivascular and other areas of edema and cellular infiltration in rabbits (a and b), and in the monkey referred to in Protocol 4: (c) in the brain, (d) in the cerebellum and (e) in the optic nerve. Modified Gram stain × 1400.

vertebral ganglia. The anterior columns of the spinal cord and gray matter of the brain were conspicuously free from lesions.

Sections stained for bacteria revealed large or small numbers of diplococci, singly and in short chains in the lesions depending on the duration of the experiment (Fig. 8, a, b, c and d). Organisms were not demonstrable in the lesions after cultures from the brain proved sterile. Edema, infiltration by polymorphonuclear leukocytes, lymphocytes and plasma cells (Fig. 7), and the streptococcus were demonstrated microscopically in the edematous areas in the sheath and between the fibers of the optic nerve in rabbits and the monkey that had developed blurred vision or blindness (Fig 8, e). No lesions were found within the eyes in such animals (Fig. 6).

SUMMARY AND COMMENTS

The results of a bacteriologic study of multiple sclerosis made by special methods is reported, and the mechanism by which an infective agent may cause a disease in which the usual manifestations of an infectious etiology are largely lacking is discussed. A green-producing or alpha type of streptococcus was consistently isolated from nasopharynx, tonsils and infected

teeth. The cardinal symptoms of this disease were reproduced or closely simulated on appropriate intracerebral inoculation in mice, guinea pigs, rabbits and monkeys with saline suspensions of the streptococcus obtained directly from the patient, with pure cultures of the freshly isolated strains, with strains after twenty or more rapidly repeated subcultures in dextrose brain broth, and with strains after one or more passages through animals.

The "spotty" distribution of the lesions in the white matter of the brain and cord, hemorrhage, edema, demyelinisation and infiltration by round cells immediately surrounding blood vessels, and other lesions in relation to vascular beds, and their similarity to the early lesions of multiple sclerosis, have been reproduced or simulated.[1] Partial or complete occlusion of vessels by thrombosis, endovascular and perivascular proliferation of, or infiltration by, lymphocytes and other cells, occurred in these experiments quite as these occur in relation to the lesions of multiple sclerosis.[2,8] and the lesions of other diseases of the nervous system.[18]

Lesions of the lungs in rabbits and mice developed not infrequently following inoculation of the streptococcus, which is in accord with the fact that the onset of the disease and especially exacerbations or extensions often follow attacks of influenza or other respiratory infections.[3,17]

The different strains isolated during the active stage of the disease were agglutinated specifically by the serums of persons stricken, by antiserums prepared with closely related streptococci, such as those from encephalitis, and by thermal antibody prepared *in vitro* from streptococci isolated in studies of multiple sclerosis.

Specific streptococcic antigen was demonstrated in skin or blood of persons in the active stage of the disease by intradermal injection of solutions of the respective closely related "natural" and specific streptococcal thermal antibodies, and specific streptococcal antibody was demonstrated by intradermal injection of streptococcal antigen. Cutaneous reactions indicating antigen were greatest during the active stage of the disease, became less marked as active symptoms subsided and as antibody increased, and both became slight or absent during the quiescent stage.

Intravenous therapeutic injections of histamine, and especially of histamine and thermal antibody as given under Dr. Horton's supervision,[3] and the thermal antibody and antigen, or vaccine without histamine, caused a diminution of antigen and an increase in antibody and apparently a concomitant improvement in symptoms in persons during the active stage of multiple sclerosis. A nonspecific and specific means for treatment seem at hand. Due regard to the prevention of respiratory infection and to a consideration of foci of infection, especially in teeth and tonsils, is indicated.

The cause of death in animals in which cultures of the brain revealed the streptococcus seemed clear, but in those that died after the streptococcus was no longer isolable from the brain or blood, and no longer demonstrable in the lesions simulating in this respect what occurs in multiple

sclerosis, the cause of death was obscure. Attempts were made to explain this phenomenon. The evidence adduced indicates that fatalities in the experimental and naturally occurring disease, in the absence of living streptococci, may be due to the formation of a streptococcic neurotoxin having predilection for vital nerve centers, and to which vital centers become allergic, and perhaps to the formation of an autogenous sensitizing streptococcal-nerve-tissue complex which may function in a manner similar to the wholly foreign adjuvant-nerve-tissue complexes used successfully by others in the production of "allergic" encephalomyelitis.[4,5]

The possibility of a virus etiology has not been sufficiently studied. The data obtained indicate that a green-producing or alpha streptococcus of low general virulence, having specific localizing, toxicogenic and antigenic properties, is etiologic in multiple sclerosis.

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RH FACTOR IN IMMUNOLOGICAL REACTIONS

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THE purpose of this paper is to present briefly some fundamental facts of importance to the field of immunology in general, which were unearthed as a result of studies on sensitization to the rhesus factor. In this preliminary report it is also intended to point out some of the applications of these findings to immunology in general, and to allergy in particular.

As is well known, the discovery of the Rh factor by Landsteiner and Wiener,[16,17] was followed in rapid succession by the demonstration by Wiener and Peters[34] of the rôle of this blood factor in the causation of intragroup hemolytic transfusion reaction, and the brilliant work of Levine, Burnham, Katzin and Vogel[5,19] in establishing the part played by the Rh factor in the pathogenesis of erythroblastosis fetalis. In these early studies, it was assumed that the antibody responsible for Rh sensitization was the Rh *agglutinins*, but it was soon found that there was a lack of correlation between the severity of the clinical manifestations and the titer of the Rh agglutinins, and in the most severe cases usually no Rh agglutinins at all were demonstrable in the patient's serum. This was incorrectly ascribed at first[20,35] to the supposed action of Rh antibodies fixed to tissue cells, but the mystery was finally solved by the discovery of the so-called Rh blocking antibody.[36,27]

As has been demonstrated elsewhere,[36,37] Rh-negative individuals sensitized to the Rh factor may produce either or both of two kinds of specific antibodies, namely, agglutinins and glutinins (or blocking antibodies). Because of their ability to clump Rh-positive cells directly, in saline as well as serum media, the Rh agglutinins are considered to be bivalent (or multivalent) in the chemical sense. On the other hand, glutinins (blocking antibodies) merely coat Rh-positive cells in saline media without clumping them and are therefore considered to be univalent. In plasma (or serum) media, univalent Rh antibodies can clump Rh-positive red cells with the aid of a third component, conglutinin, present in such media.

Based on these concepts of the nature of agglutinins and glutinins (blocking antibodies), it seemed reasonable to presume that agglutinins are comprised of larger molecules than glutinins or blockers.[38,39] This is supported by studies on the permeability of the human placenta to alpha, beta, and Rh antibodies which showed that univalent antibodies(glutinins or blockers) readily passed through the intact placenta into the fetal circulation, while agglutinins failed to traverse this barrier.[40,41] These studies were made on only a few cases, and it is proposed now to report a larger series of cases of Rh sensitization.

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A preliminary report, based on a lecture presented before the American College of Allergists on March 12, 1948.

TABLE I. COMPARISON OF THE TITERS OF RH ANTIBODIES IN THE MATERNAL SERUM AND IN THE CORD SERUM OF RH-NEGATIVE INFANTS AT BIRTH

Case No.	Titer (units‡) of Maternal Serum by		Titer (units) of Cord Serum by	
	Agglutination Method	Conglutination* Method	Agglutination Method	Conglutination* Method
1	0	20	a† 0	18
			b† 0	22
2	0	7	0	7
3	0	22	0	20
4	0	44	0	48
5	0	22	0	22
6	0	15	0	10
7	24	11	0	2½

*In albumin-plasma mixture.
†Twins.
‡The values given represent the average of the results of 2 or more titrations.

MATERIALS AND METHODS

This report is based on a series of cases in which Rh-negative women who had previously had erythroblastotic babies gave birth to normal Rh-negative babies. The maternal Rh antibody titer was determined periodically during the pregnancy, and at delivery a sample of the infant's blood was obtained from the umbilical cord vessels and another sample of the maternal blood for comparative titrations. All titrations were carried out by the saline agglutination and albumin-plasma conglutination methods, as previously described,[39,42] against group O blood cell suspensions of types Rh_1 and Rh_2 as well as control cells of type rh. Thus, the titer values given in this report represent averages of at least two titrations, and often as many as four or more titrations.

Parenthetically, it should be mentioned that in our hands the various methods of titrations used had a technical error of about one tube, or 100 per cent, when performed on different days, using test cells of different freshness and sensitivity and plasma of different conglutinating activity. Thus, a serum with a titer of 50 units might give values in different tests ranging from 25 to 100 units on different days. Therefore a four-fold difference in titer from one determination to another did not necessarily mean that there had been any real change in titer, and only by repeating titrations at frequent intervals could one overcome the misleading impression caused by such accidental variations in titer values. None of our Rh-negative patients carrying Rh-negative babies showed any significant change in titer during their pregnancies, and claims by other workers that "anamnestic" rises in Rh antibody titer can be induced by Rh-negative fetuses are possibly based on the incorrect interpretation of such illusory observations.

In a few cases, additional samples of blood were obtained at monthly intervals from the infants by venepuncture, in order to determine the length of time after birth that the maternal Rh antibodies persisted in the infant's circulation.

RESULTS

In Table I are presented the results of determinations of Rh antibody titers of the sera of seven Rh-negative women and their Rh-negative infants at the time of birth. In six cases, the maternal serum failed to clump

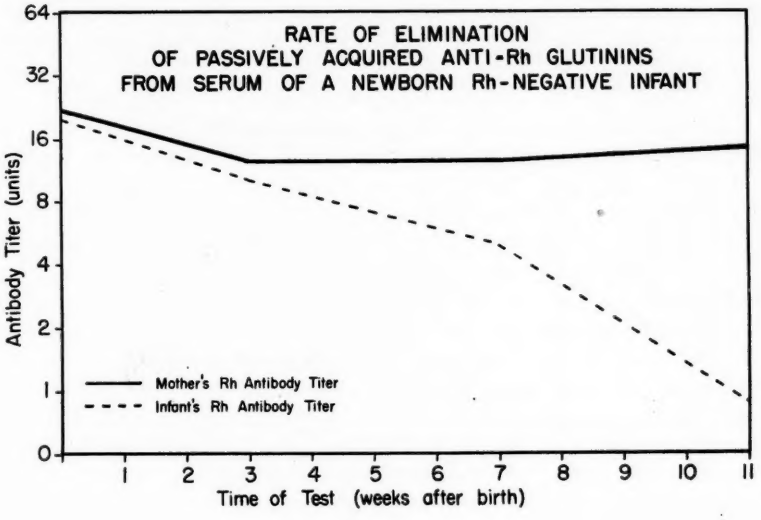

Fig. 1.

Rh-positive cells in saline media but strongly clumped such cells in plasma media, i.e., the sera of these women contained Rh glutinins with little or no accompanying Rh agglutinins. It will be seen that in these six cases the serum of each infant gave the identical titer of its respective mother's serum,* indicating that there had been a free passage of antibodies through the placenta into the fetus *in utero* until the antibody titers on both sides of the placenta became equal. Case 1 is of special interest since it involves a pair of Rh-negative twins. Case 3 is important because it involves a premature infant born six weeks before term and weighing less than 5 pounds. It will be seen that even at this early date, the fetal antibody titer was equal to the maternal antibody titer, demonstrating that, in this case at least, univalent antibodies readily passed through the placenta as early as six weeks before term, and probably considerably earlier.

In Case 7, the maternal serum contained a potent anti-Rh agglutinin, but no agglutinin was present in the infant's serum—only a very weak glutinin. Thus the placenta acts toward antibodies like a semipermeable membrane, by holding back agglutinins, but permitting glutinins (blocking antibodies) to pass freely. This supports the writer's thesis that whatever

*The excellent agreement between the titers of maternal and infant's sera is due to the performance of the tests in parallel on the same day, using the same test cells and albumin-plasma mixture.

agglutinins (bivalent antibodies) pass from mother to infant probably do so through some placental defect, and also possibly at parturition when the increased intra-uterine pressure may help to milk such antibodies into the fetus.

In Case 3, comparative studies were made of the mother's and infant's Rh antibody titers at monthly intervals after the delivery. As shown in Figure 1, there was no significant change in the maternal antibody titer during the period of four months when the studies were continued, but the Rh antibody titer of the infant's serum gradually fell so that only traces were demonstrable by the end of the fourth month. Due to lack of co-operation of the patients, similar detailed studies could not be done in the other cases. In Case 4, however, it was found that while there was no significant change in the infant's antibody titer after one month, the titers were about one-third their original values at the end of the second month. In Case 2, tests at the end of the third month showed no change in the maternal Rh antibody titer while the infant's serum contained only traces. These observations indicate that, in general, the univalent antibodies passively acquired by the infant from its mother persist in the baby's circulation for periods of about four months on the average.

SIGNIFICANCE OF FINDINGS IN RELATION TO THE PATHOGENESIS OF ERYTHROBLASTOSIS

The observations on placental transfer of Rh antibodies have served to clarify the puzzle of the pathogenesis of erythroblastosis. The offending antibody is evidently not the Rh *agglutinin*, as postulated by Levine,[19,20] but the Rh *glutinin* (blocking antibody).[37,43,44] Of course, Levine was not in a position to arrive at the complete explanation, since the Rh blocking antibody was found *after* his theory was proposed. That the univalent antibody is the important antibody is supported by recent observations which show a close correlation between titer of univalent antibodies in the maternal serum antenatally and the severity of the manifestations in the erythroblastotic fetus or baby.[8,26,29,45] The Rh agglutinins apparently play, at most, a secondary rôle in the pathogenesis of erythroblastosis, because they cannot enter the fetal circulation except through a placental defect, though a small amount may be milked into the fetus during labor as a result of the increased intra-uterine pressure.

Accordingly, the presence of Rh agglutinins in a patient's serum antenatally has significance only in indicating that the prospective mother has been sensitized, and that therefore her serum may also contain univalent Rh antibodies (glutinins or blockers) which are of importance in the pathogenesis of erythroblastosis. Cases have been encountered[46] where the maternal serum contained potent Rh agglutinins, yet the infant born, though Rh-positive, was normal or only mildly erythroblastotic. It is now clear that in these cases the maternal serum must have contained little or no univalent antibodies. On the other hand, we have encountered no

case with a significant titer of univalent antibodies antenatally, in which an entirely normal Rh-positive infant was subsequently born.

Thus, according to the new concept, the pathogenesis of typical erythroblastosis is traced to univalent antibodies in the maternal serum, with agglutinins playing, at most, a secondary rôle. This applies not only to cases caused by Rh sensitization but also to instances of A, B, Hr and other sensitizations.

SIGNIFICANCE OF FINDINGS FOR THE PROBLEM OF NEONATAL IMMUNITY

While the passive transfer of Rh antibodies from mother to fetus serves no useful purpose, but is harmful instead to the fetus with Rh-positive blood, it provides a clear though perverted example of the mechanism of neonatal immunity in general. There now seems but little doubt that whatever immunity the infant possesses during its neonatal period can be attributed to antibodies (usually glutinins or blocking antibodies and not agglutinins) passively acquired by the fetus *in utero* by transplacental transfer.† A practical application of this fact is in the antenatal selection of donors for exchange transfusions to erythroblastotic infants.[47,48] For example, group B donors may be used for group O as well as group B babies born to group B mothers, because such infants will have no beta antibodies in their sera. Another application is in the diagnosis of congenital syphilis, for which purpose serological tests on cord serum are of little value, since such tests merely constitute an indirect way of examining the maternal serum. The present study confirms other reports that the neonatal immunity passively acquired by the infant from its mother usually persists for about four to six months.[3,15,56]

In connection with this problem, it is of interest to discuss the work of Adams, Kimball, and Adams[1] who immunized expectant mothers with pertussis vaccine and then compared the antibody titers of the maternal serum and the infant's umbilical cord serum at birth. In many cases the maternal and fetal antibody titers were equal, e.g., both 320 units; in other seemingly comparable cases (maternal titer 320 units) little or no antibodies were demonstrable in the umbilical cord serum. These observations can now be readily explained by postulating that the maternal serum in the former type of case contained glutinins, while in the latter type of case the antibodies were agglutinins. Evidently, the technique used by these authors was such that it detected both agglutinins and glutinins indifferently.

If one were to inquire as to the "reason" for the infant's dependence on the maternal antibodies for its neonatal immunity, one finds that this is due to the inability of the fetus and newborn infant to produce their own antibodies, reflecting the immaturity of the antibody-forming cells during this period of life.[1,10,56] This is closely related to the observation of Lewis and Wells,[22] who showed that the blood serum of young animals

†Observations on transplacental transfer of antibodies in animals are not always applicable to man, because of anatomical differences in the structure of the placenta.[16]

is deficient in globulin, apparently because of lack of capacity to form such proteins.

The principles involved are well illustrated in a recent case of erythroblastosis treated by exchange transfusion.[49] In this case both parents were group B, and because the expectant father belonged to type Rh_1Rh_1 and the expectant mother to type rh with potent Rh blocking antibodies in her serum, the infant was delivered six weeks before term by cesarean section, and immediately treated by exchange transfusion with 1,000 c.c. of Brh blood. It was later found that the infant belonged to group O. Nevertheless, the group B blood survived normally in the baby's circulation. In fact, for a period of thirty days the only red cells present were the group B cells received by transfusion. Thereafter, the group B cells were gradually replaced by the infant's own group O cells, and it was not until four months had passed that all the group B cells had been eliminated. Even at this late date, no anti-A or anti-B agglutinins were demonstrable in the baby's serum, even though the baby had been subjected to the most potent antigenic stimulation possible, namely, the complete replacement of its own group O cells by group B red cells. A subsequent test at the age of six months still showed only barely demonstrable alpha and beta antibodies of one unit titer. This demonstrates in striking fashion the immaturity of the antibody-producing mechanism in the newborn and accounts for the dependence of the infant during its neonatal period on antibodies passively acquired from the mother. This also indicates the futility of initiating vaccine injections in newborn infants before the fourth month, in conformity with Sauer's observations.[30]

NATURE OF THE DIFFERENCES BETWEEN UNIVALENT AND BIVALENT ANTIBODIES

In the most recent edition (1946) of one of the leading texts on immunology,[52] the following appears: "The view that precipitins, opsonins, antitoxins, et cetera, differed in kind, held the field for many years, but the unitarian hypothesis that these are due to the same kind of antibody in different circumstances has now gained almost universal acceptance. . . . This conception of the serum reactions does not, of course, modify our belief in the multiplicity of antibodies corresponding to a multiplicity of antigens. A red cell, a bacillus, a crude protein solution such as horse serum, contains many antigens and gives rise to many antibodies. The unitarian hypothesis, as Zinsser (1921) has emphasized, implies that the injection into the tissues of a chemically pure antigen will lead to the formation of one antibody capable of producing various manifestations of antigen-antibody union." This quotation is repeated here since it serves to emphasize the fact that the discovery[36,37] that Rh-negative patients sensitized to the Rh factor may form two sorts of antibodies, is the first clear disproof of the unitarian hypothesis. That the significance of this evidence is not fully appreciated by other workers in the field is shown by the

TABLE II. DIFFERENCES BETWEEN "UNIVALENT" AND "BIVALENT" ANTIBODIES

Characteristics	Bivalent Antibodies	Univalent Antibodies
Common names*	Agglutinin	Glutinin; blocking antibody
Usual time of appearance in course of immunization[9]	Early	Late
Resistance to heating[9, 14, 31]	Relatively thermolabile	Relatively thermostable
Reaction with cells† in saline media	Clumps cells by agglutination	Coats cells without clumping them
Reaction with cells in plasma or serum media	Clumps cells by agglutination	Clumps cells by conglutination
Nature of clumps	Easily dislodged from glass surface	Tend to adhere to glass surface
Specificity of clumps	Specific—clumps contain only one type of cell	Non-specific—clumps may contain more than one type of cells
Rôle in erythroblastosis	Minor	Major
Reaction with cells in presence of complement[34]	Does not fix complement or lyse cells	Fixes complement and lyses cells
Behavior relative to placenta	Held back by the intact placenta	Passes through with relative ease
Role in allergy[22a, 30a]	Sensitizing antibody	Blocking antibody
Role in immunity	Precipitating antibody	Protective antibody

*Distinguishing names have not yet been devised for univalent and bivalent precipitins. As Landsteiner[18] points out, however, agglutination is equivalent to a precipitation reaction on a surface.

†Red cells, bacteria, spores and so on.

frequent use of the misnomer "incomplete agglutinins" for the univalent antibodies,[27] and the avoidance by some workers of the terms "conglutination" and "conglutinin" and the substitution of the vague expressions "agglutination enhancing action of serum" and "agglutinin activating principle in serum."

There can no longer be any doubt that univalent antibodies and bivalent antibodies are quite distinct entities, as shown by the fact that they can be sharply separated by natural means such as placental filtration.[40,41] Moreover, a partial separation of these antibodies has been effectuated by Witebsky et al,[53] using the method of dialysis in cellophane bags against distilled water. While the agglutinin proved to be associated principally with the resulting precipitate which contained most of the globulins, the blocking antibody remained mostly in the supernatant fluid together with the albumin. Incidentally, this procedure may prove of value in the antenatal diagnosis of erythroblastosis in cases where the prospective mother's serum contains agglutinins, because it may make possible the unmasking of univalent antibodies which Wiener has shown to be of major importance in the pathogenesis of erythroblastosis fetalis.** Moreover, the successful separation of the two sorts of antibodies by dialysis further supports the concept that agglutinins (bivalent antibodies) are composed of larger molecules than blocking antibodies (glutinins, univalent antibodies).

In the first papers on Rh blocking antibodies,[36,37] it was pointed out that

**A still simpler procedure, which makes use of the difference in resistance to heating of the two sorts of antibodies, has recently been devised by the writer.

the observations made were of general immunological significance and should be applicable to other antigen-antibody systems. In fact, the principles have already been applied successfully to the study of the antibodies of infectious mononucleosis,[21] brucellosis,[12] and other diseases. The major problem in further extending these applications will be to prepare satisfactory emulsions of the antigens for use in the agglutination and conglutination tests.

Since it is important to know the nature of the differences which exist between univalent and bivalent antibodies, in Table II the present information and concepts regarding this aspect of the problem have been summarized. Some of the references given are to the older literature, which has been reinterpreted in terms of the newer concepts.

OTHER APPLICATIONS IN IMMUNOLOGY

The newly available information regarding univalent and bivalent antibodies can be applied to the solution of a number of problems.

1. For a long time it has been observed that there is only an incomplete correlation between the titer of the isoagglutinins, alpha and beta, and the ability of the serum to lyse specifically red cells containing agglutinogens A and B, respectively, so that occasionally sera with low agglutinin titers lyse such cells while some sera with relatively high agglutinin titers fail to lyse such cells.[47] This is now readily understood, since the isoagglutination reaction is attributed to alpha and beta *agglutinins* (bivalent antibodies), while isohemolysis is ascribed to alpha and beta glutinins (univalent antibodies) in the presence of complement. Some correlation between agglutinin titer and isohemolysis is to be expected, because the sera with the most potent agglutinins will usually be derived from immunized individuals and would therefore be more apt to contain strong glutinins.

2. In studies on treated syphilitic mothers who were subsequently delivered of nonsyphilitic infants, different investigators have obtained conflicting results when comparing the reagin content of the maternal and umbilical cord sera.[28] This is now readily explained by differences in the methods of titrating syphilitic reagin used by the different investigators. Where complement fixation methods (detecting univalent antibodies) are used, the titers obtained for maternal and infant's sera would be expected to be equal, but where methods are used which detect principally bivalent antibodies the newborn's serum may show little or no reagin despite a high titer in the maternal serum.

3. To account for the pathogenesis of acquired hemolytic anemias, the writer[47] has suggested that in rare susceptible individuals, when an acute breakdown of red cells occurs, as in sulfonamide therapy, benzene poisoning, malaria, certain influenzal infections (virus attached to red cells), trauma (hematomata), et cetera, the released stromata act as antigens and induce the formation of auto-antibodies which act on unaltered red cells.

This produces more hemolysis, and the hemolyzed cells in turn induce more antibody formation so that a vicious cycle results. Luckily, such auto-immunization is extremely rare, and hemolytic injuries are usually self-limited in their effects. In the rare susceptible individual where auto-sensitization results, recovery is very infrequent. In support of this hypothesis may be cited a number of cases[4,33,50] in which it was possible to demonstrate in the patient's serum auto-agglutinins which differ from the natural auto-agglutinins in that they are equally active at body, room and refrigerator temperature, while the natural auto-agglutinins are cold agglutinins. Until recently, however, it was not possible to demonstrate the presence of auto-antibodies in the great majority of cases of hemolytic anemia, and this has now been explained because auto-antibodies like other antibodies may be of the univalent type. The univalent auto-antibodies coat the patient's own blood cells so that a condition results which simulates that which exists in erythroblastotic infants. Coating of the patient's cells by auto-antibodies can readily be demonstrated by the same techniques used for the diagnosis of erythroblastosis fetalis, namely, the conglutination test[38] and the antiglobulin test.[25,32,46] In malaria this process accounts for the rare complication of "blackwater fever," or if the cells clump by conglutination instead of hemolyzing, death from cerebral malaria may result, a syndrome somewhat analogous to nuclear jaundice in the erythroblastotic infant.

The natural auto-agglutinins are qualitatively different from the immune auto-antibodies, and the former probably depend on certain peculiarities of normal serum globulin as against immune globulins. The rise in cold auto-agglutinin titer associated with virus pneumonia therefore probably reflects an increase in the normal serum globulins due to nonspecific irritation of the antibody-forming cells. The hemolytic anemia[2,11,55] that sometimes results when the cold auto-antibodies are of such high titer that they also react at body temperature differs from the acquired hemolytic anemia described above in that complete recovery is the rule, following simple transfusion therapy.[46]

4. In the conglutination test for coating of erythrocytes by univalent antibodies (Rh antibodies, auto-antibodies, or antibodies of other specificities), all that is necessary is to suspend the cells in plasma or albumin-plasma mixture and spontaneous clumping results because the conglutinin present in the plasma is adsorbed by the sensitized cells and completes the reaction.[38,45] The antiglobulin technique depends on a different principle,[6,7,24,51] namely, the use of a rabbit precipitin against human serum which reacts with the human globulin (the specific univalent antibody) coating the red cells, thus causing them to clump together. It is not generally appreciated that the antiglobulin reaction is an agglutination reaction, and if the precipitin serum contains univalent antiglobulin antibodies instead of bivalent antibodies, the test may fail. The intelligent application of the

newer knowledge of univalent and bivalent antibodies is therefore essential for the successful use of the antiglobulin technique.

APPLICATIONS IN ALLERGY

In closing, some possible applications of these newer concepts to some problems in allergy, especially the pathogenesis of infantile eczema, will be pointed out, with the hope that this may stimulate new investigations which may help solve this enigma.

The work of Sherman, Hampton and Cooke[30a] leaves hardly any doubt that the skin-sensitizing antibodies are bivalent antibodies, while the blocking antibodies of allergy are univalent antibodies (Table II). Thus, these workers found that skin-sensitizing antibodies do not pass the placental barrier, while blocking antibodies pass through freely into the fetus. That the failure of maternal skin-sensitizing antibodies to pass into the fetus is not due to fixation of the antibodies by the placenta is indicated by the observation that placental extracts are free of such antibodies. Loveless[22a] showed that skin-sensitizing antibodies (reagins) are thermolabile, while blocking antibodies are relatively thermostable. Moreover, Cooke, Løveless and Stull[7a] found that maternal blocking antibodies passively acquired by the infant disappear from its serum within three to six months, while the antibodies disappear from the maternal serum much more slowly. The parallelism between the observations in the fields of allergy and Rh sensitization further justify the term "Rh blocking antibody" in preference to other terms, such as "incomplete Rh antibody," that have been suggested by other workers.

Based on these observations and in line with the newer concepts, the following definitions are offered.[13,52]

1. The normal (nonallergic and nonimmune) state is that in which the body contains no *induced* antibodies specific for the antigen in question. Cognizance is taken of the possible presence, however, of so-called natural or normal antibodies.[18]

2. The immune state is one in which the body has acquired large amounts of antibodies of the blocking type, formed in response to the introduction of antigen into the body by either natural or artificial means, so that there is an excess of univalent antibodies free in the plasma and other body fluids.

3. In the allergic state, the body contains sensitizing (bivalent) antibodies attached to cells, with little or no free univalent antibodies in the body fluids. Reagin represents excess bivalent antibodies free in the body fluids.

4. Hyposensitization is the process of converting the allergic state into the immune state by repeated injections of antigen at sufficiently wide intervals to stimulate the production of potent blocking antibodies. This treatment is successful only when the subject achieves an adequate level of free univalent antibodies in his or her body fluids.

5. Desensitization consists in the injection of progressively increasing doses of specific antigen in rapid succession in order to saturate antibodies attached to body cells. This method, besides being dangerous, is often unsuccessful, and the refractory state that ensues is only temporary due to the subsequent production by the body of additional antibodies.

Before describing the application of the newer concepts to infantile eczema, some other pertinent observations will be presented. Experiments[46] with the production of anti-Rh typing sera, by injecting Rh-positive blood into Rh-negative male volunteers, reveal that the majority of those who respond show only univalent antibodies (glutinins or blockers) in their sera, while only a small minority produce agglutinins. Moreover, when the injections are continued any agglutinins which may have been formed are eventually largely or completely replaced by blocking antibodies. Thus, bivalent antibodies, if they are formed at all, are usually produced only early in the course of the immunization. Once a person has been sensitized to the Rh factor, and the antibody titer has fallen with the passage of time, the injection of a relatively minute amount of antigen is usually sufficient to elicit a pronounced antibody response. In line with this, Cooke, Loveless and Stull[7a] found that normal subjects required much more pollen extract (200,000 to a million units) to produce blocking antibody than hay-fever patients sensitized to ragweed (total 4140 units).

Previous studies have revealed that the predisposition to allergic diseases is hereditarily transmitted. In persons homozygous for the abnormal gene, the age of onset is usually in the period before puberty, and these individuals make up the bulk of the cases of infantile eczema and asthma.[51a] That the effect of the abnormal gene can be modified follows from the observation that twice as many males as females develop allergic disease before puberty. In persons heterozygous for the abnormal gene, allergy may never appear in typical form (carriers), but about one-fifth of these individuals exhibit allergic symptoms usually after puberty—these constitute the bulk of the cases of hay fever.[51a]

The mother and also the father of the baby with infantile eczema are therefore themselves allergic or at least carriers of the abnormal gene. For example, in cases of infantile eczema due to sensitization to wheat, the constitutionally predisposed infant, when fed foods containing this antigen produces bivalent (sensitizing) antibodies for wheat. While the infant's mother will usually be hyposensitive to wheat, any univalent antibodies against wheat passively acquired by the infant by placental filtration will have been lost by the third or fourth month, when it is likely for the first time to produce its own sensitizing antibodies. This would account for the delayed onset of infantile eczema, usually until several months after birth. Permanent cure of this disease takes place only when the infant's body is stimulated, either by natural or artificial means, to produce wheat antibodies of the blocking type, so that an excess of these antibodies is

again present, free in the body fluids. The eventual production of such antibodies accounts for the spontaneous cure of infantile eczema, usually by the time the second year is reached.

It is too early to discuss other applications of these new concepts in the field of allergy, until more accurate quantitative data are compiled concerning the titers of reagin and blocking antibody in different allergic conditions. For this purpose, the classic method of titration using increasing antigen dilutions is not satisfactory, because antibody titers can be determined reliably only by testing increasing dilutions of serum against a fixed quantity of antigen.

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CLINICAL EVALUATION OF NEOHETRAMINE, A NEW ANTIHISTAMINE

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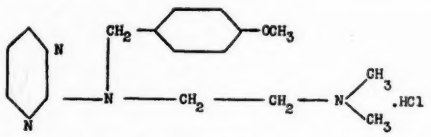
A GREAT deal of literature has accumulated in recent years on the action of the new antihistaminic drugs. It is generally recognized that they control various allergic manifestations, notably those of urticaria and vasomotor rhinitis. They appear to counteract such action of histamine as whealing, bronchospasm, secretion of salivary and bronchial glands.

We have had occasion to carry out clinical trials with Neohetramine,* a new compound. This is an ethylenediamine derivative, highly soluble and relatively stable in aqueous solutions. Its chemical formula is 2-(N-dimethylaminoethyl-N-p methoxybenzyl)-aminopyrimidine monohydrochloride.



EXPERIMENTAL DATA

Laboratory experiments carried out by Scudi, Reinhard and Dreyer[1] generally followed the procedures devised in evaluating other antihistaminic drugs. Guinea pigs and rabbits were fully protected against otherwise lethal doses of histamine. The drug was administered intraperitoneally fifteen minutes before aerosol insufflation of histamine into the bronchi and, in other experiments, before intravenous injections of histamine. Neohetramine prevented anaphylactic shock in actively and passively sensitized guinea pigs. It counteracted the fall in blood pressure ordinarily encountered from intravenous injections of histamine as well as dilatation of capillary blood vessels. In comparison with other antihistaminics tested, Neohetramine appeared to be of low toxicity.

CLINICAL OBSERVATION

Observations were made on 279 allergic patients. In selecting these cases for the clinical trial, an attempt was made to exclude those who exhibited evidence of secondary infection. It had been noted before that infection, superimposed upon the allergic symptoms, reduced the benefit obtained from antihistaminic drugs considerably. Some of the patients were observed in the clinic for several hours after they had taken the drug; in most cases, however, our conclusions were based on careful questioning within one to two days after the treatment was started. Doses of 50 mg. were employed at four-hour intervals. The patients were instructed to take the

From the Allergy Clinic, Out-Patient Department, Harper Hospital, Detroit, Michigan.
*Supplied by Nepera Chemical Co., Inc., Yonkers, N. Y., and now distributed by Wyeth, Inc.

drug only when symptoms were present. Nearly all had previously had other antihistaminic medication and were able to compare the new drug with them. Forty-eight patients received placebo tablets containing ¼ grain of phenobarbital, alternating with the new drug in order to enable us to evaluate the possibility of a psychogenic effect from the drug.

TABLE I

Diagnosis	Total	Results			
		None	Slight	Good	Side Effects
Bronchial Asthma	75	42 (56%)	20 (27%)	13 (17%)	9
Allergic Rhinitis and Hay Fever	165	52 (32%)	50 (30%)	63 (38%)	17
Urticaria	21	3	6	12	—
Migraine	5	2	2	1	—
Atopic Eczema	6	2	2	2	1
Contact Dermatitis	2	2	—	—	2
Allergic Conjunctivitis	5	3	2	—	—
Total	279	106	82	91	29 (10%)

Table I presents our results. Where the drug was effective, the improvement started within thirty minutes and lasted approximately four to six hours. After this interval, symptoms recurred.

Urticaria and allergic nasal disease showed the best results. Eighteen (86 per cent) out of twenty-one patients with urticaria and 113 (68 per cent) out of 165 patients with a seasonal and perennial allergic nasal disease were benefited. In the group of patients with asthma, thirty-three (44 per cent) out of seventy-five showed some degree of improvement. Only three (13 per cent) out of twenty-one patients with urticaria and fifty-two (32 per cent) out of 165 with seasonal and perennial allergic nasal disease were not benefited. On the other hand, in the group of patients with asthma, only thirteen (18 per cent) showed some improvement. In the other allergic conditions in which the drug was employed, namely, atopic eczema, contact dermatitis, migraine headaches and allergic conjunctivitis, too few patients were treated by us to draw definite conclusions. It is evident, however, from Table I that the results simulate closely those obtained with other antihistamine drugs.

In twenty-nine (10.4 per cent) out of 279 patients, side effects were encountered which resembled those observed with the other drugs. The side effects, however, were less frequent. Dizziness and drowsiness were most prominent. Several patients presented muscular twitching about twenty minutes after ingestion of the drug, which disappeared spontaneously in approximately one hour.

One of our patients (Mr. F. R.) with urticaria, was given 50 mg. of the following six drugs on successive days in the office: Neo-Antergan, Trimeton, RP-3277, Antistine, Benadryl and Neohetramine. Within one-half hour following the ingestion of each, he developed marked drowsiness and sleepiness. During his sleep he exhibited marked muscular twitching of the limbs and trunk, which at times resembled epileptic attacks. This lasted for

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DERMATOPHYTOSIS AND FUNGUS SENSITIVITY

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DUE to the relative increase both in severity and in number of cases of dermatophytosis and dermatophytids seen during the past year, our interest was stimulated in the search for a more satisfactory treatment. The long list of accepted local therapeutic measures did not offer the gratifying results that ordinarily we would have expected from close observation and control of our patients. No one method of local therapy seemed to be uniformly successful. In many, a great variety of medications had to be used in order to obtain any results. Often during the long tedious process of determining the effective therapeutic agents, the patient suffered a spontaneous remission of the disease. In most instances, the patient soon returned with a recurrence of the disease.

A number of the patients presenting themselves for treatment were veterans of World War II, which is not surprising in view of the American Medical Association's report by the Council of Pharmacy and Chemistry, "The War and Dermatophytosis,"[1] in which it was revealed that 8 per cent of all army hospital admissions were for cutaneous disease and that dermatophytosis ranked second highest as cause for these admissions.

Delaney[4] feels that about 80 per cent of all personnel stationed in the South Pacific area for more than three months contracted a fungus infection of some type.

Almost universally, these patients had histories of long-standing infections with special reference to their primary lesion. Most had developed the secondary dermatophytids which appeared of greater severity than the primary lesion. In a number of cases the "id" (dermatophytid) lesions were of such nature as to cause a definite disability and a major physical disfigurement. The "id" lesions are variable in presentation but are generally characterized as erythematous, irregular, papular or vesicular lesions, nodular in the more acute stages, becoming more eczematoid or psoriatic-like in the chronic form. In a few cases where the "id" lesions were severe, the primary lesions, usually on the hands or feet, were concomitant causes of complaint.

It has been our experience that a patient will present himself with a history of having been treated with at least ten different types of local medications plus an unsuccessful course of x-ray therapy. These patients have developed a strong psychogenic complex because their chronic lesions do not seem to respond to the best of available local therapy in spite of their eager co-operation.

There seems to be no question that dermatophytosis has been a thera-

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peutic problem for many years, and there are many reports consistent with the findings of Weidman,[29,30] showing that 67 per cent of 100 medical students were infected and had primary lesions which yielded positive cultures in 57 per cent. A more recent survey reported by Lewis and Hopper[16] of 1,399 cases, revealing positive slides in 46 per cent and positive cultures in 67.3 per cent. These surveys and those of Duemling,[5] Delaney,[4] Montgomery and Casper[18] also illustrate that the offending organisms in the majority of cases are the trichophytons, with the epidermophytons ranking second and the monilias third. Over an eleven-year period, 1935 through 1945, at the New York Skin and Cancer Unit, 17.9 per cent of the 1,706 positive cultures were isolated from lesions of the feet, and 30.5 per cent of the 331 taken from the hands were of the Trichophyton group of fungi.

With a large proportion of our population returning to civilian status from service with the armed forces, many of whom were in tropical areas, it is possible that the evolution of this clinical entity can result in a grave medical problem should the present trend continue.

Having these thoughts in view, it became obvious that this disease had to be approached from the immunologic point of view. Although the fungi are ubiquitous in nature, there seems to be no question that they are abundant, are etiologic agents and can cause cutaneous disease. The Association of Allergists on Micrological Investigation[31] has uncovered a variety of fungi which are definitely causative factors of allergic disease. It is unfortunate to contemplate that comparatively little work has been directed toward these universal and abundant pathogens. Extensive surveys have been reported by Durham,[6,7] Feinberg and Little,[10] Wittich[32] and others. It has been proven that fungi are not only air-borne so as to cause hay fever and asthma, but are also found abundantly in the smuts and rusts. These same fungi can and do cause serious dermatologic lesions.

Even though the fungi are not considered virulent pathogens, they can be transferred from human to human as well as from animals to humans and thus can cause the spread of disease, reaching epidemic proportions. Many types of fungus dermatoses are endemic in various parts of the United States. Dermatophytosis can be a grave disease and is of serious import. Other fungus diseases, such as actinomycosis, histoplasmosis and blastomycosis, can be fatal.

The immunologic aspect of fungus infection has been known for some time. The work of Low,[17] Block,[2] and Jadassohn and Peck[14] has been confirmed, giving evidence that a skin hypersensitivity develops to the fungi of the trichophyton group quite constantly when these organisms are present in superficial tinia infections of the hands and feet. There seems little question that fungi can cause chronic eczematoid lesions, as shown by Hilgermann[12] and confirmed by more recent work of Hopkins, Benham and Kesten,[13] who found a definite sensitization to saprophytic

fungi in deep-seated eczematoid lesions. Brown[3] skin-tested patients with chronic eczemas and found them sensitive to a variety of fungi; the lesions cleared up when the fungi were eliminated from the environment or were specifically treated. Skin lesions, according to Henrici[11] are typical characteristics of hypersensitivity in fungus diseases.

Sulzberger,[23] working in Block's clinic, has demonstrated that there is a spontaneous passage of formed elements (spores) of fungi originating from the primary lesions by hematogenous dissemination. These formed elements can cause eczematoid lesions in the skin. In a later work, Sulzberger and Kerr[24] illustrated that hypersensitivity to trichophyton is a "group specific" in human beings and that it occurs exclusively in persons who have or have had tinia infections. Sholtz,[21] as well as Sulzberger[25] found that tests with products of one fungus in this group will give positive results even though the infection has been actually caused by another member of this same group. As an example, a patient suffering from a ringworm infection, from which is cultured *Epidermophyton inguinale*, can react to injections of an extract prepared from *Trichophyton interdigitale*. The same relationship exists between the epidermophytons, trichophytons and microsporons. Sulzberger[25] revealed at this time also that the organisms of the trichophyton group do not react with the monilia group. Only those lesions due to the monilia react to a monilia extract.

In this broad way there is a differential activity in the development of skin sensitization. Patients having fungus lesions develop antibodies present in the circulation which can be demonstrated by their ability to be passively transferred to the skin of normal nonsensitive individuals, thus revealing the existence of specific antibodies or reagins. In a further work, Sulzberger and Lewis[26] illustrated the fact that a trichophyton hypersensitivity can be elicited by means of contact or patch tests using an extract of the fungi.

With this wealth of immunologic evidence bearing upon the close relationship between the sensitivity to fungus extracts in patients having a fungus infection, it is surprising that an immunologic method has not been used more extensively in the treatment of this disease. Attention should be directed to this method of approach, since the "id" lesions often are more serious to the patient than are the primary lesions. The "id" lesion is an allergic manifestation and, therefore, should be prone to more efficient treatment by immunologic methods. It has been common experience that local therapy only aggravates the "id" lesion rather than cures it.

In the ordinary course of events, the development of the "id" might be outlined as follows: From the primary lesions spores are released into the blood stream which travel throughout the body. These spores will reach the skin which has been sensitized; and there, in reaction to the products of the fungi, an eczematoid lesion develops. The spores lodging in other organs which have not become sensitized cause no lesions apparently. Since sensitization is one of the primary factors in the develop-

TABLE I.

NO.	PATIENT	AGE	SEX	ASSOC. ALLERGY	LESION	DURATION YEARS	IDENTIFIED & CULTURED	SKIN TESTS (SCRATCH): ACHORION 3.	ASPERGILLUS 6.	ASPERGILLUS 7.	EPIDERMOPHYTON 1.	HELMINTHOSPORIUM	HORMODENDRUM	MICROSPORUM 1.	MONILIA 4.	MUCOR pl.	PENICILLIUM 11.	RHIZOPUS NIGRA	TRICOPHYTON 2.	TRICOPHYTON 5.	TRICOPHYTON 7.	CHAETOMONIUM	ALTERNARIA 9.	NO. OF INJECT.	RESULTS	REMARKS
1	C.E.	28	F		HANDS & FINGERS	1/2	NEG.-b	0	+	0	0	0	0	0	+	0	0	0	0	+	0	0		30	MARKED IMPROV.	
2	J.V.T.	6½	F	G.I.-V.M.RHINITIS	HANDS	1	NEG.-b	+	0	+	0	0	0	0	+	0	0	0	0	0	0	+		39	CURED	LAST 16 INJECT. 0.05 CC.
3	L.A.	6	F		ANKLES	1	EPIDERMOPHYTON	0	0	0	0	0	0	+	0	0	0	0	0	0	0	0		49	MARKED IMPROV.	LAST 15 INJECT. WEEKLY
4	J.O.	48	M		HANDS & FINGERS	7	TRICOPHYTON	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		20	MARKED IMPROV.	WEEKLY INJECT.
5	E.C.	50	M	URTICARIA - G. I.	HANDS, LEGS, ANKLES	1	EPIDERMOPHYTON	0	0	0	0	0	0	0	0	0	0	0	+	0	0			29	MARKED IMPROV.	LAST 5 INJECT. 1/100,000
6	R.E.	8	M	ASTHMA - H.F.	FACE, FINGERS, FOOT	1/12	EPIDERMOPHYTON	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		3	IMPROVED	STOPPED TREATMENT
7	R.K.	7	M	ASTHMA - H.F.	FEET & TOES	3	NEG.-b	0	0	+	0	+	0	0	+	0	0	0	0	0	0	+		5	CURED	
8	J.M.	14	F	ASTHMA - H.F.	FOOT, ELBOWS	1/2	NEG.-b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		27	CURED	LAST 22 INJECT. WEEKLY
9	H.N.	63	F		HANDS & FINGERS	10 +	MONILIA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		33	CURED	
10	A.O'L.	32	F	HAY FEVER	HANDS & FINGERS	5	NEG.-b	0	0	0	+	0	0	+	+	0	0	0	0	0	0	0		11	CURED	
11	E.P.	23	M		HANDS & FINGERS	4	MONILIA	0	0	0	+	0	0	+	+	0	0	0	0	0	0	0		61	MARKED IMPROV.	20 INJECT. OF 0.2 CC.
12	M.P.	11	F	URTICARIA	GENERALIZED	3 1/12	NEG.-b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		17	CURED	
13	R.W.	66	M		LEG & FOOT	2	NOT IDENTIFIED	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		54	MARKED IMPROV.	LAST 24 INJECT. 0.2 CC. VARICOSE VEINS
14	A.G.	16	F		HANDS, FINGERS, ANKLE	2	TRICOPHYTON	0	0	0	+	0	0	+	0	0	+	0	0	+	0	0		17	CURED	
15	J.H.	40	F		HANDS & FINGERS	20 4/12	NEG.-b	+	0	0	0	0	0	0	0	0	0	0	0	0	0	0		12	UNIMPROVED	4 INJECT. 1/100,000 DISC. TREAT.
16	A.M.	22	F		HANDS & FINGERS	5/12	NEG.-b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		8	IMPROVED	DISCONTINUED TREATMENT
17	E.M.	54	F	URTICARIA, H. F.	HANDS, FINGERS, LEGS	2 3/12	EPIDERMOPHYTON	0	+	0	0	+	0	0	+	0	0	0	0	0				38	MARKED IMPROV.	
18	T.P.	3	M		FEET & TOES	2	ASPERGILLUS																	15	CURED	
19	E.K.	29	F	V. M. RHINITIS	HANDS & FINGERS	5	PENICILLIUM C.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		29	UNIMPROVED	VARIED DILUTIONS & INTERVAL
20	R.C.	40	M	URTICARIA	GENERALIZED	2/12		0	0	0	0	0	0	0	0	0	0	0	0	0	+	0		5	CURED	
21	M.M.	59	F	ASTHMA	HANDS, LEGS	3																		6	MARKED IMPROV.	VARICOSE VEINS
22	M. S.	61	M	URTICARIA	HANDS	10		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		22	MARKED IMPROV.	SLIGHT RECURRENCE
23	E. H.	33	F		HANDS & FINGERS	2 1/2		0	0	0	0	0	0	0	0	+	0	0	0	0				49	MARKED IMPROV.	
24	J.V.	50	M	V.M. RHINITIS	HANDS & FINGERS	3		0	0	0	0	0	0	0	0	0	0	0	0	0				11	CURED	
25	L.F.	26	F	V.M. RHINITIS	HANDS & FINGERS	6		0	0	+	0	0	0	0	0	0	0	0	0	0				18	IMPROVED	0.5 CC. 1/100,000
26	M.G.	54	M	URTICARIA	FEET & TOES	20	NEG.-b	0	0	0	0	0	0	0	0	0	0	+	+	0	0			34	MARKED IMPROV.	
27	C.S.	41	M		CHEST & FEET	3	EPIDERMOPHYTON	0	0	0	0	0	+	+	0	+	0	+	+	0	0			11	MARKED IMPROV.	
28	C.L.M.	59	F		HANDS & FEET	10	TRICOPHYTON	0	0	0	0	0	0	+	+	0	0	0	0	+	0			8	CURED	
29	W.M.	28	M	URTICARIA	HANDS	11		0	0	0	0	0	0	0	0	0	0	+	+	0	0			8	CURED	
30	M.M.	32	F	URTICARIA	EARS	5	MONILIA	0	0	0	0	0	0	+	0	0	0	0	+	0	0			7	MARKED IMPROV.	

ment of the "id," it would seem probable that this chain of events could be made reversible or else broken by means of desensitization.

Sulzberger and Wise[27] have tried desensitization with good results. They treated over 100 cases, although only nineteen are reported, with the conclusion that the longest apparent cures were obtained in treating these fungus lesions with fungus extracts. Robinson and Grauer[20] used autogenous fungus extracts in the treatment of mycotic lesions and had very encouraging results. Schonwald[22] states that, in dermatomycosis, the allergic state is definitely responsible for tissue injury and consequent inflammatory reaction. The ultimate healing is also due to their allergy.

Fungi of the monilia group are strong sensitizers[15] and capable of producing primary skin infections and secondary eczematous eruptions. They resemble closely the trichophyton group. Since a good percentage of fungus infections of the hands and feet are due to the monilia group, and, furthermore, since the trichophytons and the monilias do not interreact, Pennington[19] used separate injections of the trichophyton and monilia extracts in twelve cases with a reported cure of nine, one improved, and no results in two. In another series of twenty-one cases, she attempted hyposensitization with fungus extracts, with the result of curing twelve, improving five, no results in three, and in one a doubtful result. Of 100 reported cases by Van Dyck et al, 81 per cent were improved or cured. Recently, Epstein[9] reported the successful use of fungus extracts in the treatment of dermatologic eczematoid lesions in the aged. His results were obtained using a low concentration (1:10,000 dilution) of a fungus extract given intradermally in doses from .05 to 0.1 c.c. every fifth day. Schonwald[22] also reveals excellent results in the treatment of the trichophytid lesions as well as the primary focus, using low dilutions of fungus extracts. Few investigators report any serious reaction to the use of the fungus extracts. These fungus extracts apparently are very effective in very low dilutions and only small amounts need be given.

Accordingly, with this background, we have attempted to treat a series of epidermophytoses and epidermophytid cases using a fungus extract* containing the *Trichophyton gypseum, Trichophyton interdigitale, Epidermophyton inguinale* and *Monilia albicans* in a dilution of 1:5,000. It is quite evident that since all these fungi do not interreact, that a composite mixture had to be made in order to cover the most common causative fungus factors.

METHODS AND RESULTS

In Table I, thirty patients are presented who were followed for a period of about a year. All have received previous local therapy. In addition, many had received a course of x-ray treatment. The majority were clinic patients. Ages ranged from three to sixty-three years.

Sex distribution is not particularly significant, since more females, 56.7

*The Arlington Chemical Co., Yonkers, New York.

per cent in this series, are seen, generally, in clinic practice. However, the male attendance, 43.3 per cent, is relatively high. This may indicate that the men made a special effort to come in for treatment because of the severity of their lesions.

The average duration of the chief complaint was 4.82 years with a history, in almost all, of a primary ringworm infection of the feet. Dermatophytid lesions appeared universally on the extremities and, in a few, on the face, ears and body.

TABLE II

Epidermophyton	5
Trichophyton	3
Monilia	3
Aspergillus	1
Penicillium	1
Not Identified	1
Positive Cultures	14

An associated allergy or history of allergy was found in 56.7 per cent. Of these, almost one half were receiving treatment for their other allergy. The possible effects of such collateral treatment, in this series, is a matter for discussion. It is felt that this point is more of academic interest rather than of practical significance. These patients continued to have the "id" lesions for a long time, and these lesions did not clear even though other allergy was controlled. A clinical impression was gained that, while the skin lesions were clearing up, the present treatment did not contribute to a better control of other allergy, except in a nonspecific way psychologically.

This high incidence of associated allergy is significant in that there is a greater likelihood that sensitization to the offending fungi will occur, and more probably that the persisting skin lesions are also allergic manifestations.

Of the 93.3 per cent skin tested (scratch method), 64.3 per cent were found positive to dry fungus extracts. This high percentage of skin positives is significantly greater than the percentage (56.7 per cent) of previously known allergic persons. This would indicate that a hypersensitivity does develop in persons not known to be allergic. Probably, the percentage of positive reactions would have been higher if intradermal injections of trichophyton extracts were used. The scratch method was chosen because it is deemed expedient, safer, more easily controlled and actually is a more severe criteria of skin sensitivity.

Of the 76.7 per cent cultured, 56.5 per cent were accurately identified as to the causative organism. The lesions selected for culture were from locations which presented the greatest physical disfigurement. This was done purposely for the psychological benefit of the patient whose anxiety was usually fixed on these areas. Cultures were obtained at the time of the initial history and physical examination. Table II reveals the types and incidences of the causative fungi isolated.

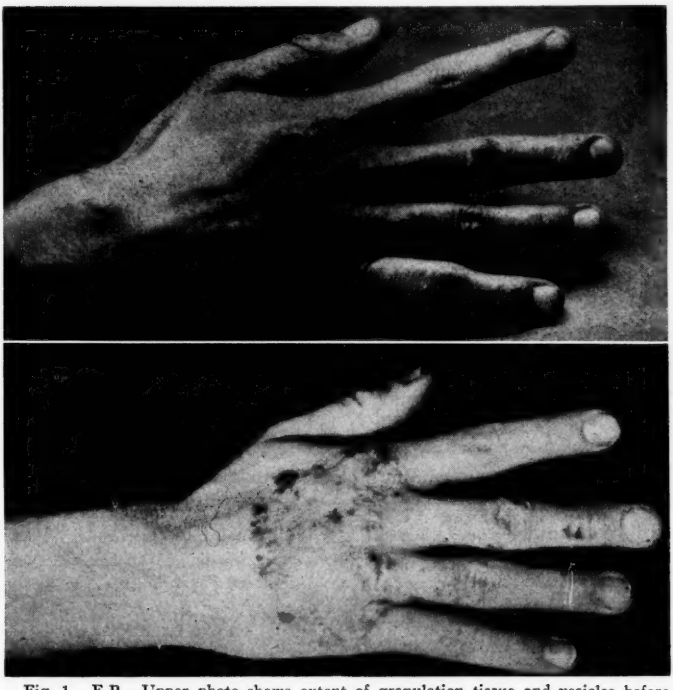

Fig. 1. E.P. Upper photo shows extent of granulation tissue and vesicles before treatment. Lower photo shows response after twenty injections.

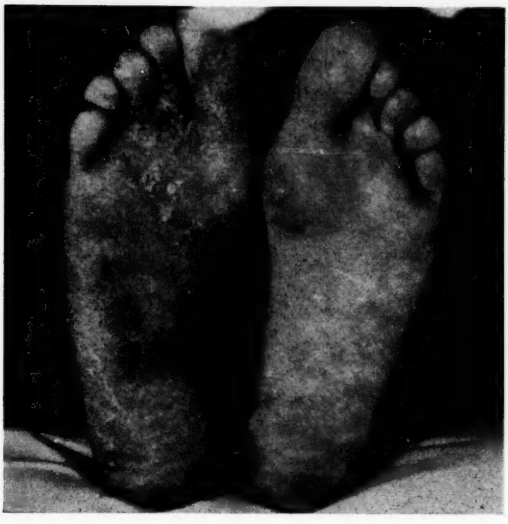

Fig. 2. M.P. Lesions on feet which were part of a generalized distribution.

A culture was obtained in the following manner: The lesion was swabbed with alcohol, and a drop of serum from the vesicle or scraping of a licheniform lesion was used to inoculate the culture medium.

In the early portion of this investigation a broth culture medium was used made up as follows:

Water	12 liters
Peptone	120 grams
Cerelose	240 grams
Salt	60 grams
Yeast extract	12 grams

This medium was chosen because it was used commercially and yielded flourishing growths. However, in this experience, only the bacterial contaminants seemed to multiply. The cases in which this broth medium was used are indicated in Table I as Neg.-b. It is unfortunate that this collateral data was lost because, while waiting for growth and identification of the organism, the patient improved so markedly that subsequent cultures were negative.

In the remaining cases, a standard Sabouraud's agar slant was used. The inoculated culture tubes were allowed to remain at room temperature for two weeks. At the end of this time, there was generally sufficient growth present for identification.

A dilute extract was chosen in order to start desensitization at a low enough level to accommodate even the most sensitive without causing a reaction. It is our clinical judgment that excellent results can be obtained with the use of dilute extracts rather than quickly trying to give the most concentrated extract the patient can tolerate. The immunologic responses can be adequate, and desensitization is accomplished with a therapy employing dilute extracts.

Each patient received a dose of 0.1 c.c. of the extract intradermally twice a week. This schedule was attended by good results. In some patients, the regime was varied slightly as indicated under "Remarks" in Table I. In very sensitive patients, the extract was further diluted, as shown, or a smaller dose given. In those who had improved markedly, the interval between injections was increased to one week, which was usually done at the request of the patient.

In two patients, an attempt was made to increase the dosage in order to shorten the course of therapy. It was found that if more than 0.2 c.c. was injected intradermally, local necrosis would result, with the skin over the wheal sloughing off. This was confirmed many times when sterile saline was injected in equal quantities as a control. Apparently, human skin can accommodate a wheal of 0.2 c.c. as a maximum before the local circulation is disturbed.

No serious reactions were seen after injection, although there were occasional and temporary (a) flaring up of the lesion, (b) local reaction

at the site of injection associated with a mild lymphadenitis and (c) pruritis.

Generally, pruritis soon disappeared after the initiation of treatment. In the early part of the course of injections, pruritis might return on the day before or the day when another injection was due. In other words, the patients were asymptomatic for a period of three to four days following injection. After a few more injections, pruritis disappears. Occasionally, a patient reveals focal flare-ups in the beginning of treatment, which may be part of a hypersensitivity phase before the desensitization effects take place.

A therapeutic regime consisting of an average of 22.5 injections gave the following results:

Cured	40.0%
Marked Improvement	43.3%
Improved	10.0%
Nonimproved	6.7%

These attainments are consistent with those of Van Dyck[28] and Eller[8] wherein 80 per cent or more of patients treated were markedly improved or cured.

Any method of therapy which gives such a high percentage of good effects should be vigorously recommended and adopted.

Any patient who presents himself with a chronic eczematoid lesion, with a history of an associated allergy, who is skin-positive to fungus extracts and from whose lesion a fungus organism can be identified, should receive desensitization as the treatment of choice.

SUMMARY

Thirty cases of fungus dermatoses are presented, with their relationship to allergy and fungus sensitivity illustrated. Etiologic organisms were cultured and identified. Better than 80 per cent were markedly improved or cured after a desensitization regime using a small intradermal dose of a mixed fungus extract.

Acknowledgment and thanks are offered to Seymour L. Shapiro and Emmanuel Murrow of the Arlington Chemical Co., Biological Laboratories, for their co-operation and assistance in the identification of the fungi cultured.

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CLINICAL EVALUATION OF NEOHETRAMINE

(Continued from Page 306)

about one and one-half to two hours. He remained free from hives for at least twelve hours after ingestion of each drug.

Five patients were followed for over three months, during which time blood pressure readings, blood counts and urine examinations were taken every two weeks in order to determine any possible ill effect. There were no significant variations in these tests.

(Continued on Page 321)

PAROXYSMAL DYSPNEA

Case Report

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THE patient, M.S.W., was referred to me by Dr. J. R. Jordan of Washington, D. C. A white woman, aged seventy-five, was admitted in September, 1945, with a diagnosis of asthma.

Family History: Her father had hay fever. There was no other familial allergy.

Past History: At the age of eight or nine, she was confined to bed for eight months with an attack of acute rheumatic fever which affected the heart. Consequently, she was unable to play tennis or dance during her childhood and early womanhood. At the age of sixty-six, cataracts were removed. Six years later, she was hospitalized for two months with "flu" and pleurisy. She had otherwise enjoyed good health during her long life. Her present illness was of four years' duration. The first attack awakened her out of a sound sleep. She was unable to breathe. Her distress was so acute as to necessitate the injection of epinephrine. The attack was accompanied by a generalized eruption of hives of moderate size.

For four years, similar attacks had been of daily occurrence. They usually began at dusk, although they sometimes occurred in the afternoon when she was overtired. Hives had continued to accompany the attacks. An occasional hive, however, had appeared independently of respiratory distress. As many as four attacks had disturbed the sleeping hours. The attacks were perennial and non-seasonal. Vasomotor signs, cough and expectoration were absent. Tightness of chest, slight wheezing, dyspnea and orthopnea comprised the important symptoms. Frequently, she had been obliged to sit up in a chair before an electric fan. She stated, moreover, that the upper portion of her back was very sensitive to touch.

Four years previously, she had consulted an internist and allergist. Tests for protein sensitization had revealed a positive reaction with house dust extract. Aminophylline by mouth, phenobarbital and the continued injection of epinephrine had been prescribed by the consultants.

She remained under observation at the Doctors Hospital from September 17 to 28, 1945. Her temperature ran a normal course. The minimum pulse rate was 68, and the maximum 100 beats per minute. On only three occasions did the pulse rate exceed 90. Respirations averaged 20 per minute. The relevant findings, determined by physical examination, were as follows:

Weight, 100 pounds; height, 61¼ inches.

Head: Depression over temperal fossae, indicative of her weight loss of 30 pounds during her illness. *Neck:* Moderate distention of cervical veins. Supraclavicular and suprasternal fossae markedly sunken. *Lungs:* Inspection—expansion equal. Palpation—tactile fremitus normal. Percussion—unsatisfactory. Very light percussion over the back caused wincing. Percussion over the anterior chest elicited a normal note. Auscultation—breath sounds normally vesicular. Râles absent. No respiratory wheeze. Vocal resonance normal. *Cardiovascular system*—Heart normal in size and position. Sounds regular, first sound weak. The pulmonic second accentuated. Harsh loud systolic murmur heard over the precordia. The radial pulses synchronous and equal. All heart beats transmitted. The popliteal and dorsalis pedis pulses palpable. Blood pressure 170/80. *Abdomen*—Slight distention. No masses palpable. Rigidity and tenderness absent. *Extremities*—Edema absent.

Tests for protein sensitization were performed by the cutaneous method with epidermal and miscellaneous proteins, representative pollens, molds, and food pro-

teins with negative results. Intracutaneous testing with the more common allergenic extracts proved negative, also.

Blood examination—Hemoglobin, 76 per cent. Red cell count, 4,010,000 per cu. mm. White cell count, 5,900 per cu. mm. Differential count: Neutrophiles, 59 per cent; eosinophiles, 10 per cent; basophiles, 0 per cent; monocytes, 1 per cent, and lymphocytes, 30 per cent. The urinalysis was normal.

The electrocardiographic report is as follows: Rate 92. Regular rhythm, left axis deviation, T waves upright in all leads. P.R. interval, .14 seconds. QRS complexes normal. Impression: Left axis deviation.

Roentgenological examination on the third day following admission showed marked increase in fibrosis throughout both lungs, not inconsistent with the patient's age. There was no evidence of any infiltrative process in the lungs. There was some calcification in the right apex, which was stable in appearance and of no clinical importance. The heart was normal in size and contour. There was no widening of the aortic arch. There was a small calcified plaque in the transverse portion of the arch.

The dorsal spine showed marked productive changes at the ante ior margins of the vertebrae and marked thinning of the intervertebral discs. The appearance was that of an osteoarthropathy of the hypertrophic type.

On several occasions, a study of the patient was made during an acute attack. She sat upright in her chair. Her expression was anxious. The breath sounds were scarcely audible, interrupted at times by a sigh. Neither the respiratory rate nor pulse rate were accelerated. On auscultation the respiratory murmur was diminished in intensity. No musical râles were heard. Especially noteworthy was the absence of wheezing and noisy breathing and of the intensive pumping effort, characteristic of the acute asthmatic seizure. An injection of epinephrine subcutaneously promptly relieved the distress.

Analysis of the clinical picture was indicated. It will be recalled that the diagnosis on admission was asthma. On the one hand, the positive family history for allergy, the intermittent eruption of hives, the eosinophilia and the favorable response to epinephrine suggested a disturbance allergic in origin. On the other hand, the negative results of the tests for protein sensitization, the roentgenological examination, electrocardiogram and the dyspnea without wheezing were not revealing of the nature of the mechanism involved.

A critical review of the symptomatology was necessary. Shortness of breath would come on at any time during the day and required no medication. Shortness of breath invariably appeared before the completion of dinner at six o'clock, and attacks of dyspnea recurred during the night. She was "afraid to eat and sleep." Of special significance was the patient's statement that she experienced a "clutching feeling in the region below the left breast," after her dinner "has been down only a minute." At times, this region was sensitive to touch.

The advent of symptoms after the large meal of the day, and the "clutching feeling" and tenderness of the anterior lower left chest pointed to an involvement of the upper portion of the digestive tract. The resulting dyspnea after eating suggested an interference with respiration due to external pressure exerted upon the lungs. The tentative diagnosis of a diverticulum of the esophagus in the thoracic portion was justified by anatomic and physiologic considerations.

On September 24, 1945, seven days after admission, the findings of an examination of the digestive tract with bismuth disclosed the following: The esophagus showed deviation towards the right in its lower third. This was due to the presence of a large hiatal hernia of the stomach. Aside from the presence of the hiatal hernia, the stomach was quite normal in appearance. There was no deformity at the pylorus nor of the cap.

With the recognition of the disturbed relationship between the organs of the thorax and of the abdominal cavity—a relationship not entirely unsuspected—the

question of surgical intervention inevitably presented itself. One surgeon of the younger school recommended repair of the hernia. Another surgeon of the older school did not approve of any radical operative procedure because of the advanced years of the patient.

The patient returned home. Suppositories of aminophylline and dilaudid hydrochloride were prescribed to supplement the injections of epinephrine. The ingestion of small frequent meals and the curtailment of starchy foods was likewise recommended.

It is noteworthy that the patient had included a "slight wheezing" in her list of symptoms. Consulting physicians had suggested the diagnosis of asthma. Is it possible that in the case under discussion the asthmatic state is present and is independent of the hiatal hernia?

On repeated examinations, the absence of musical râles and wheezing has been striking—even at the height of an attack of dyspnea. Agreement is universal that, in asthma, spasm of the bronchi is produced by the muscular contraction of their walls. In this connection, the observations of Henry Hyde Salter, made many years ago, remain unchallenged. He states: "We know in health that respiration is noiseless, but that when the breathing becomes asthmatic it is accompanied with a shrill sibilant whistle. We know, too, that hollow tubes give no musical sound, when air rushes through them, if they are of even calibre, but if they are narrowed at certain points, if their calibre is varied, the air in them is thrown into vibrations, and they become musical instruments. The wheezing of asthma, then, is as positive evidence of bronchial contraction as if we could see the points of stricture—it is physical demonstration."

If this criterion be applied to our patient, the diagnosis of asthma cannot be confirmed.

During the four years of incessant attacks, various medicaments had been employed. A total number of thirty-four capsules of Benadryl, in divided doses of 50 mg. each, failed to relieve. The injection of epinephrine had always proved dependable when suffocation threatened. No evidence had thus far been adduced to prove that bronchospasm was primarily the cause of the dyspnea. If, therefore, the surmise be correct that the dyspnea was the direct result of pressure by a distended stomach upon lung tissue, the relief from distress afforded by epinephrine merits an explanation. In the treatment of asthma, epinephrine has ranked first in importance. The stimulation of the terminations of the bronchial sympathetic fibres by epinephrine causes a relaxation of the musculature within the walls of the tubes. Consequently, the bronchi become widely dilated, and a greater volume of air is admitted to the alveoli of the lungs. This pharmacological action takes place in the normal as well as abnormal lung.

It may not be amiss to make inquiry into the causes of diaphragmatic herniation. They are three in number: (1) congenital, (2) traumatic, and (3) acquired. The first two causes can readily be excluded.

Hernias of the acquired type, however, tend to occur in adult life. They are secondary to small defects in the diaphragm and result from strain. It will be recalled that a sudden attack of dyspnea during sleep first signalled the invasion of the thoracic cavity.

Our patient was unaware of any unusual physical strain prior to her present disability. Accordingly, the relaxed state of muscular organs, frequently encountered in very old people, may have been a contributing factor to the formation of a hernia through a weakened or defective diaphragm.

The patient again sought help and consultation in March, 1947, eighteen months after her hospitalization. She was approaching her seventy-seventh birthday. She continued to survive her increasing distress. Her present complaints depicted the underlying pathologic conditions. She felt weaker. The attacks of shortness of breath were more frequent and more severe. More medication was required during the day.

There was very seldom any distress after breakfast, which consisted of two or three slices of toast, eggs, and two cups of coffee. She ate very little lunch. In the evening, shortness of breath would come on before the end of dinner, accompanied by the "clutching feeling" in the region of the left lower chest. She then required

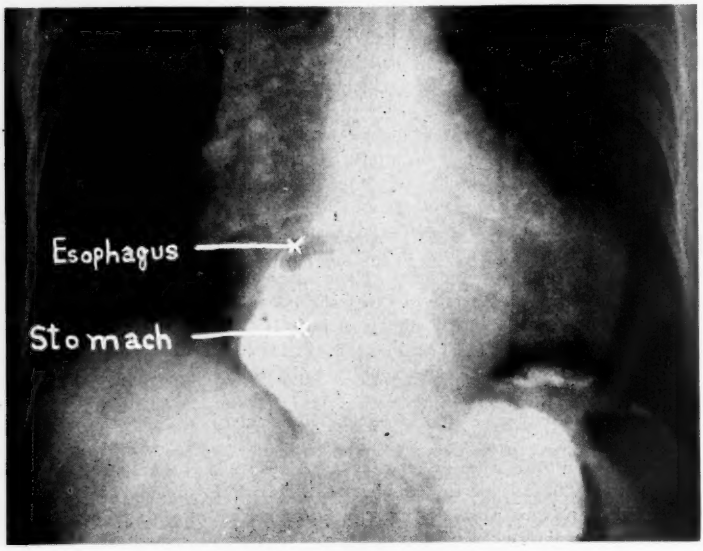

Fig. 1. Radiograph taken on March 20, 1947.

epinephrine immediately. She needed at least four injections of 5 minims of epinephrine daily, followed by a tablet of phenobarbital. After the injection of epinephrine, she experienced some "rumbling" in the abdomen. Eructations were rare. A slight cough usually preceded an attack, and there was practically no expectoration. Hives had been absent for one year. The pain and tenderness which had been confined to the upper dorsal area had become more widespread. At times, the pain was very sharp under the shoulder blades.

The following symptoms assumed significance: (1) During the past several months, when aroused from her sleep by an attack, she had noticed coughing and wheezing—more than ever before. (2) She was experiencing pounding of the heart on occasions.

On physical examination, the area of cardiac dullness was enlarged. The apex measured 4 inches from the midsternal line in the sixth interspace. The systolic murmur was transmitted to the left axilla. The pulse rate varied from 74 to 78. The systolic pressure registered 160 mm.—a slight decrease from the earlier record. Edema of the extremities was absent. When observed during a daytime attack of dyspnea, the patient stated that she felt as if she had been running. The respiratory movement appeared labored and scarcely audible. Musical râles and wheezing were not present.

Five attempts were made to determine her vital capacity. She was most reluctant to take a deep breath and blow into the spirometer. She feared the effort would bring on an attack.

A control roentgenological examination was made on March 20, 1947. The findings were as follows: Examination of the chest showed the following heart measurements: M.R., 5.1 cm.; M.L., 9.7 cm.; total, 14.8 cm.; chest, 23 cm. Hence, the heart was markedly enlarged to the left and to a small extent to the right. There was the usual fibrosis along the bronchial tree which is seen at this age period.

Examination of the upper gastrointestinal tract showed an esophagus which was deviated to the right and entered a large hiatal hernia (Fig. 1). This was approximately 6 cm. in diameter and of about one-third the capacity of the stomach. The esophagus seemed probably shorter than normal but the abnormality of contour was considered due to the hiatal hernia. The diaphragm moved freely. The stomach was otherwise normal in appearance.

A comparative study of the x-ray plates revealed a marked increase in the size of the heart, chiefly of the left side. Cardiac function as evidenced by pulse rate, absence of edema and cyanosis seemed unimpaired. Nevertheless, the nocturnal cough and nocturnal wheezing and occasional pounding of the heart may justify the diagnosis of a cardiac asthma of recent onset.

The movements of the two sides of the diaphagm were studied with the fluoroscope in the late morning before lunch. Their free and equal movements despite the possible embarrassment of the herniated stomach are noteworthy. This observation is of importance in excluding the presence of an intrabronchial growth or foreign body, as an unforeseen complication.

SUMMARY

A patient, now in her seventy-seventh year, with a diaphragmatic hernia involving about one-third of the capacity of the stomach, has been seeking relief from an allergist because of some allergic implications and complications.

REFERENCE

1. Salter, Henry Hyde: On Asthma—Its Pathology and Treatment. P. 35. London: John Churchill, 1860.

ACKNOWLEDGMENTS

It is my pleasure to record my thanks to Drs. Arthur C. Christie and Fred O. Coe for their roentgen reports and to Dr. Fred A. J. Geier for his electrocardiographic study.

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CLINICAL EVALUATION OF NEOHETRAMINE

(Continued from Page 316)

SUMMARY

Neohetramine, a new antihistaminic drug, was used to treat 279 persons. The results compared favorably with corresponding observations on other antihistaminic drugs. Side effects were rare, but should be reckoned with as in all antihistaminic therapy. The best results were obtained in allergic nasal disease and urticaria.

REFERENCE

1. Scudi, J. V.; Reinhard, J. F., and Dreyer, N. B.: Pharmacological characteristics of Neohetramine, a new antihistaminic drug. III. J. Allergy, 19:184-199, (May) 1948.

10 Peterboro
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Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

ON THE EDITING OF PAPERS

The ability to advance knowledge by scientific investigation and the capacity to put the description of the resulting factual material into readable language are not necessarily or universally present in the same individual. Readers of ANNALS OF ALLERGY are invited to take part in a discussion (by letter) concerning the functions of the editors.

On the one hand, should the editors limit themselves to the mere correction of possible factual inaccuracy? To follow this course would result in the publication of some papers, excellent in fact but bad in grammar and worse in style. To quote McDaniel,+ "His selection of papers, the knowledge that they are factually reliable, his judgment in the matter of accessory material, his taste in the make-up of the journal, should obtain for the editor all the recognition he should properly seek. He is not or should not be a schoolmaster." To this school belong those who believe that if a man is literarily inept, so much the worse for him. Let him appear to his fellows and posterity as he is.

On the other hand, have the editors other duties? As objective arbiters should they not make certain that all the gold has been mined; that the facts have been put forward to their best advantage; that the prolix be made more succinct and the overbrief, more detailed? Are the facts not more important than the man? To present them in their best light acquires for them in their utmost clarity the widest acceptance consistent with the deepest understanding.

In other words, is the man to be respected more than his work or are the facts above the personality? Is it possible to insist that contributions be made concise and clear without fear of offense, or must we tread warily for those who resent the transposition of a comma, however misplaced? Shall we reject papers that are poorly written or shall we accept everything as is, if factually valid?

As the writer of the paper or its reader, which do you prefer? Please tell us.

+McDaniel, W. B.: Letter to the Editor. Science, 106:491, 1947.

Progress in Allergy

HAY FEVER
A Review of the Literature of 1947

MORRIS A. KAPLAN, M.S., M.D., F.A.C.A., and NORMAN J. EHRLICH, M.S., M.D., F.A.C.A.
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In the last year, some 150 papers dealing with hay fever and related problems appeared in the world's literature. The great bulk of the papers dealt with the new group of chemical compounds which were originally introduced as "antihistaminics" but which we now recognize better-termed as "antiallergics." A year has passed, and a true clinical evaluation of this group of substances is now a part of the literature. Many articles have appeared, dealing with pollen surveys, method of surveys, pollen purity, chemistry, immunology, diagnostic methods, attempts at standardization, therapy including prophylactic, specific and nonspecific methods, all of which will be included in this review. It is with deep regret that the opening statement of our last year's report,[56] which stated that "to the worker in allergic problems, the preparation and standardization of pollen extracts is of prime importance; the lack of uniformity and agreement in these matters is disturbing," is as true today as it was then.

BOTANY AND POLLEN SURVEYS

Durham,[25] technical director of the committee of the American Academy of Allergy on national pollen surveys, reported the adoption of a standard factor for volumetric conversion of ragweed gravity slide counts obtained with the standard technique. This factor is equal to 3.6, and is arrived at by averaging the catch of ragweed pollen on one square centimeter of slide exposed in the standard instrument, compared with the average catch per cubic yard of air by a simultaneously operated and independently calibrated volumetric sampler. The sampling apparatus devised by O. C. Durham, is simple, easy to make, and inexpensive when purchased.

This method, accepted by the National Pollen Survey Committee of the American Academy of Allergy, is not the last word for evaluating the quantity of pollen in the air over a twenty-four-hour period, due to the fact that many factors enter into pollen distribution any time during the day and night, as temprature, wind velocity, humidity, and sudden changes in barometric pressure. Durham[25] calls attention to this in his article, in which he discusses spot testing. In summarizing his studies, he states that by the use of the Hill dust pump or his so-called Air Whip, which is a 36-inch aluminum rod for swinging a slide in a circle with the oiled face forward, he is able to make spot tests under variable conditions. He was able to test the allergen-producing ability of sixty plant species and several fungi. As a result of repeated spot testing of the air in the immediate vicinity of small plants, small plots, or extensive acreages, some very striking figures for maximum production have been obtained. With the usual gravity tests, a pollen count of 5,628 per cubic yard of air is recorded against 9,600,000 per cubic yard of air by the spot method. In another test by the routine gravity method, a hormodendrum count was recorded as 20,000, compared to 869,000, by the spot method. This report discusses the amount of air contamination under various meteorological conditions, and explains the marked variation in pollen counts as reported by the usual twenty-four-hour average gravity slide method.

In conjunction with Durham's work, a large number of the allergists[131] located in and around the metropolitan district of New York, undertook a survey of ragweed pollination during the 1946 season. They used the technique recommended by the pollen survey committee of the American Academy of Allergy, staining the slide by the Calberla stain, using a cover slip of 2.2 cubic centimeters square, and counted under low power. The number of granules per square centimeter in twenty-four hours was equal to the number of pollen grains counted, divided by 4.84. The pollen grains per cubic yard was equal to that number times 3.6. In summarizing, they stated that the pollen counts in New York City were rather low in 1946, and the highest counts, in order, were Brooklyn, Flushing, Manhattan, Rockaway, Ozone Park, Queens, Bronx, Staten Island. It was felt that the pollen counts in Manhattan were most representative of the city as a whole. It was also noted that the peak occurred at about the same time in each one of the stations.

A similar survey was carried out by Kailin[54] in the District of Columbia, using the methods described above.

Werner, Reed and Stormfels[134] report a pollen survey conducted in 1945 at Albuquerque, New Mexico. The gravity method of collecting pollen was employed. Stations were set up from 4 to 40 feet above the ground level. Four hay-fever seasons were noted, with the major season extending from April 13 to October 28. The spring season, from February 12 to May 7, produced the highest counts, with Juniper, cottonwood, and Bermuda grass as the prime offenders. The summer season extended from May 7 to August 7, with Bermuda grass, Russian thistle, and plantain in large amounts. The fall season extended to the first week of November, with Russian thistle, pigweed, and false ragweed as the chief offenders. Pollen counts as high as 1,400 were recorded during the spring, with counts below 100 for the summer and fall seasons.

Stroh,[121] in his article on pollens of the Northwest, divided those pollens found east of the Cascade Mountains and those along the coastal region. In the Northwest, there are three pollen seasons: the tree season beginning in March and lasting well into May; the grass season beginning in May and lasting through July; and the weed season beginning sometime early in May, but mostly in June, and lasting well into September. The coastal area contains a greater number of offending pollens than the area east of the Cascade Mountains.

Jennes, in collaboration with the National Pollen Survey Committee of the American Academy of Allergy, using the standard sampling device and the standard method, reports a three-year study carried out in Waterbury, Connecticut. The pollen counts for the three-year study were correlated. None of the counts were very high.

Walton and Dudley,[129] reporting on hay fever in Manitoba, in the *Canadian Medical Association Journal,* state that there are three pollinating seasons. The spring season begins the latter part of April and continues to mid-June, the summer season begins in late May and continues until mid-July; the fall season begins in late July and continues until early September. The spring season is due to the pollens of trees, namely, the poplar, elm, Manitoba maple and oak, willow, birches, and alder. The summer season is due to the pollen of the bluegrass, timothy, June, and redtop grasses. The fall season is due to the weeds, namely, giant, western, and perennial ragweeds, burweed marshelder, Russian thistle, Kochia and sages.

Several reports on pollen surveys from foreign investigators have been reported. David Ordman,[87] discussing pollinosis in South Africa, stated that there are a number of trees, grasses, and weeds that are important. Eighty per cent of all pollen extract preparations are used in the grasslands. In South Africa the season begins in June and lasts until October. The common tree offender is the cypress, although in some areas the pepper tree is important. The common grass is that commonly known as the Cosmos, and of the weeds, those belonging to the Compositae family, and the khaki weed, are most common.

In discussing allergic diseases in Palestine, Lass[61] stated that cases of seasonal hay fever are comparatively few, in contrast to perennial vasomotor rhinitis, the incidence of which is very high. Bermuda grass, which grows perennially, was the chief offender. It was noted that the Palestine atmosphere carries a strong scent of citrus fruits in April and May, and is a known cause of nasal catarrh. He further stated that there have been no exhaustive pollen studies in Palestine similar to those done in the U. S. Although mold extracts are used in testing patients, there has been no systematic survey.

Atmospheric contamination by mold spores has frequently been reported as a factor in producing hay-fever symptoms. Alternaria and hormodendrum are the two molds which have been chiefly incriminated. Deamer and Graham[21] reporting an atmospheric survey from the San Francisco area, showed that 59.5 per cent of the mold colonies cultivated were due to hormodendrum, as compared with 2.4 per cent alternaria and 19.2 per cent penicillium. It is interesting to note that there was no striking seasonal incidence of mold spores, making the diagnosis of clinical mold sensitivity difficult.

Froughtman[39] reported from Barcelona that aspergillus, penicillium, cladosporium, and alternaria were the most important molds noted in his survey. Relatively higher counts were observed in the harbor area of the city.

Nilby,[85] the first to use the Petri method of mold identification in Sweden, conducted his survey from August to December, 1946. The greatest concentration occurred in the last days of August with an increase in misty weather. The concentration was low during the winter, but even in severe cold weather, spores were found in the air. The common outdoor fungi were penicillium, pullalaria, and yeast-like fungi. Penicillium, the most common indoor fungus, did not show seasonal fluctuation. Other fungi found in homes were those belonging to the alternaria and the monilia groups. Exposure of plates in large and small cities, country and rural areas, indicated that the greatest mold concentration occurred in the smaller cities and rural areas. The highest spore counts were noted in barns and threshing mills.

Seltzer,[111] in a paper, "Pollen Counts—Their Proper Place in Hay Fever," discussed the weaknesses of pollen counting and the inaccurate deductions that are drawn from the twenty-four-hour glass slide pollen counting method.

Wallis[128] reported on "Peat, Hayfever and Pharmacognosy." From his studies of pollen granules in geological formations in Great Britain, the clinically effective pollen season runs from early March until late September. This period can be divided into three phases: (1) tree pollen, (2) grasses, (3) dicotyledonous barks.

King and Brooks,[59] in an article on the terminology of pollination, felt that there were four major categories of pollination: (1) within an individual flower, (2) between flowers of the same plant; (3) between flowers of different plants of the same variety (where varieties are recognized) or species; and (4) between flowers which are on plants belonging to different varieties or species.

IMMUNO CHEMISTRY

Abramson,[1] by means of the moving boundary method of electrophoresis of Tiselius, ultra-centrifuge, precision diffusion techniques, isolated highly purified fractions of pollen extracts, and found that the molecules responsible for clinical pollen hay fever and asthma were not large protein antigens, but ones of comparatively low molecular weight, of the order of 5,000 or less, with chemical properties similar to, but not characteristic of, proteins. Preliminary studies indicate that the pollen extracts are complex mixtures of many components with, however, a main colorless component readily isolated by means of the electrophoretic technique. The main colorless component of giant ragweed has been named Trifidin, that of the dwarf ragweed, Artefolin, and that of timothy extract, Pratensin.

Abramson has introduced a new term in describing these substances, because they have some chemical properties resembling protein; however, they are different from ordinary proteins. The name he has suggested is the term protoproteins. A protoprotein would be a substance on the border line between the higher molecular weight polypeptides and the low molecular weight proteins. It is hoped that by the use of the methods described above and chemical studies, immunologic data will be more valid, since antigens would be pure and not multiple complexes.

We concur with Abramson when he stated that pollen extracts are not simple antigenic solutions, but complex mixtures containing many components that are biologically active. How then is one justified in insisting that chemical standardization procedures properly assay the biologic activity of pollen extracts? Furthermore, that the protein nitrogen as assayed by the phosphotungstic acid precipitate method represents not only the inactive but the equally active biologic skin fraction. Furthermore, to measure the allergic activity of a pollen extract by only a biologic response like the skin test, using complex mixtures, is also open to scrutiny. The chemical determination of total nitrogen, and the further evaluation by studying its biologic activity, seems to us to be the best method of standardization available to us at the present time. If and when the chemical characterization of the purified fractions can be studied by immunologic methods, the interrelationships between chemical and immunologic activity, as well as ability to produce sensitization and protection, will then lead us to more accurate methods for standardization.

A number of articles dealing with the chemical and immunologic specificity of various fractions from ragweed pollen extract, have been reported this year. Among these studies is the report of Sherman and Stull[113] adding further evidence of the immunologic specificity of fractions 1 and 2. In summarizing their results, they found that the reaction of fraction 1 and fraction 2 of low ragweed pollen, with ragweed-sensitive serum in passive transfer, showed evidence of the independent specificity of the two fractions. With one serum, fraction 1 was 1,000 times as reactive as fraction 2, while with another serum, fraction 2 was 100 times as reactive as fraction 1.

Ragweed-sensitive patients treated with the separate fractions, developed specific antibodies to the fraction injected. Serums of rabbits injected with fraction 1 showed specific reactions with this fraction in precipitin tests, passive sensitization of guinea pigs, and passive sensitization of human skin. Only one of the three rabbits injected with fraction 2 developed precipitins, but these were specific for fraction 2. In both man and rabbits, fraction 1 was a more active antigen than fraction 2. The preparations of fractions 1 and 2 were described in previous papers of these authors.

Baldwin et al,[4] reporting on their studies of the chemistry and immunology of low ragweed pollen extracts, prepared their fractions by serial alcohol precipitations of aqueous low pollen. This was followed by chloroform treatment, as suggested by Sevag, as a method of separating proteins from carbohydrates. In their discussion, they noted that this work was undertaken with the hope that, in the field of atopic sensitivity, a study of ragweed might reveal some immunologic specificity of the nitrogen, or of the carbohydrate (polysaccharide) fraction, similar to that shown by investigators for bacteria. They compared the immunologic activity of three fractions of low ragweed pollen extract prepared by serial precipitation with alcohol, and treatment with chloroform with that of standard pollen extract. Fraction B contained approximately 7 per cent nitrogen and 14 per cent carbohydrate; fraction D contained approximately 5 per cent nitrogen and 58 per cent carbohydrate, and fraction S contained approximately 1.4 per cent nitrogen and 60 per cent carbohydrate, and gave a negative ninhydrin test. Standard pollen extract and fractions B and D, but not fraction S, were precipitated *in vitro* by rabbit antiragweed serum. Standard pollen extract and fraction B, but not the others, were also pre-

cipitated by rabbit antifraction B serum. No precipitations were observed with rabbit antifraction D serum. Sensitization of guinea pigs to standard pollen extract was produced with each fraction. Sensitization to fraction B was produced with all fractions except fraction S. Sensitization to fraction D was produced only with fraction D. No sensitization to fraction S could be produced. Studies of untreated ragweed-sensitive persons showed that the threshold of sensitivity, for skin and conjunctiva to standard pollen extract, was lower than to any of the three fractions. Fairly strong evidence was presented, indicating that the carbohydrate fraction of low ragweed pollen extract is not a very active antigen, since, while it sensitized guinea pigs to whole ragweed extract and elicited positive reactions in untreated ragweed-sensitive human beings, it failed to produce precipitins in rabbits. The further the attempts to purify and fractionate the original ragweed pollen extract were carried out, the less striking and consistent were the immunologic reactions observed. Immunologic reactivity diminished with a decrease in the nitrogen content of the fraction.

Stone, Harkevy and Brooks[120] reported their studies on the chemical investigations of giant ragweed pollen. Their method of preparation was, first, defatting giant ragweed, and then extracting with distilled water for twenty-four hours in the refrigerator. Three similar extracts were thus prepared. The extracts were combined and concentrated. The material was then diluted and dialyzed for fourteen days. The dialysates were combined and evaporated. The active material in the dialysates is heat stable, and not denatured at an interface. The dialysate was then precipitated with trichloracetic acid. The filtrate, after complete precipitation with trichloracetic acid, was then treated with picric acid, and after complete precipitation, the resulting filtrate was treated with phosphotungstic acid.

In summarizing their results, they stated that when an aqueous extract of defatted giant ragweed pollen was exhaustively dialyzed, about one-half of its allergenic activity appeared in the dialysate. The active principle in the dialysate was heat-stable and not denatured at an interface. The dialysate was further purified by treatment with trichloracetic acid. After the removal of that precipitant, saturated picric acid was added, and then the excess eliminated. Neither treatment precipitated the active principle, nor was the skin reactivity of the extract appreciably changed. Phosphotungstic acid precipitated the active principle. Upon getting rid of the insoluble addition compound of the phosphotungstic acid, thereby making it soluble again, the activity was recovered. The most highly purified fraction yielded a positive ninhydrin, biuret, and Molisch test.

Stevens[117] studied the quantitative changes in various fractions of the precipitable nitrogen in ragweed extracts during incubation at 37° Centigrade. Their data showed a decrease in the nitrogen precipitated at half and full saturation with sodium sulphate at 37° Centigrade. The phosphotungstic acid precipitate also showed a decrease. The analyses suggest a degradation of protein molecules to split products of lesser magnitude, to a point where they are beyond the level of effective precipitants.

Alexander, Johnson and Bukantz[2] studied thermostable antibody titers as determined by the precipitation methods. They found that there was a general lack of correlation between thermostable antibody as determined by the methods used, and the degree of clinical protection. The mechanism by which clinical improvement occurs following specific pollen therapy, remains unknown.

Brown et al,[14] studying the response of the blocking antibody to oral pollen therapy, showed that there was no correlation between increase in antibody titer to clinical symptomotology, and therefore finally concluded that there was no correlation between skin test, eye test, antibody titer, and clinical results.

Urbach[125] and his associates, in a discussion of the chemical and immunologic basis of oral pollen propeptan therapy in hay fever, gave as evidence of the specificity of their preparation, the fact that it protects a highly sensitized guinea pig against

a multiple lethal dose of pollen antigen. They also showed that the pollen propeptans retain their type-specific immunologic properties when tested by the Prausnitz-Küstner reaction. If animals that had been sensitized to pollen by the oral or bronchial or intravenous route, and had been hyposensitized by pollen propeptans, were then attempted to be shocked by pollen, no reactions occurred, thus indicating protection. The results of these investigations seemed to constitute, to these authors, experimental confirmation of the therapeutic value of specific pollen propetane therapy in hay fever in man.

Swineford, Houlihan, and Robinson,[122] studying antibodies for ragweed extract, could not confirm the observations of Cohen and Weller's preliminary report of the demonstration of precipitins in the sera of treated, and not in untreated, ragweed-sensitive patients. Neither the thermostable antibody nor reagin could be titrated when human sera were mixed with collodion or parlodion or other particles which had been sensitized by ragweed extract. Antiragweed rabbit serum agglutinated ragweed-sensitized collodion and parlodion particles consistently. Normal rabbit serum controls, properly prepared, were negative.

Squier and Lee,[115] in a discussion of the lysis *in vitro* of sensitized leukocytes by ragweed antigen, summarized their results by stating that polymorphonuclear leukocytes obtained from heparinized whole blood of patients sensitive clinically, and by skin tests, to ragweed pollens, were studied, following the addition of short ragweed antigen to the heparinized blood. Lysis *in vitro* of these sensitized leukocytes was evidenced by reduction of approximately 43 per cent of the total number of cells. The disintegration of leukocytes was inhibited by heating for one hour at 56° Centigrade, presumably by inactivating the ragweed-sensitizing antibodies. No significant change in the total number of leukoyctes occurred after the addition of ragweed in bloods inactivated by this technique. No significant reduction in the number of leukocytes occurred after the addition of ragweed antigen, in the manner described, to unheated blood samples of ragweed-sensitive patients treated adequately by injections of ragweed antigen.

Miller and Campbell[80] gave a preliminary report on the experimental evidence in support of a new theory of the nature of reagins. Reaginic sera of egg-sensitive patients were added to crystalline ovalbumin in varying dilutions, and incubated at room temperature for two hours. Rabbit antiovalbumin serum was then added, and the mixture incubated at room temperature for two hours, and at 4° Centigrade for forty hours. The precipitate obtained was analyzed for protein by the Folin-Ciocalteu method. It was found that the reaginic sera increased the amount of precipitate. Reaginic serum from pollen-sensitive individuals, employed as a control, failed to produce an increase in the amount of protein precipitated. It was concluded that the reagins in egg-sensitive serum are in some way incorporated in the ovalbumin-rabbit antiovalbumin precipitation.

An interesting paper by Rhoden and Sutherland,[100a] of Australia, on the chemical nature of a protein-free preparation of egg white, linseed, and castor bean, recalls the work of Grove and Coca, Black and Moore, who asserted that the active fraction of pollen is a carbohydrate. After a comprehensive review of the literature on this subject, Newell stated that the general opinion held by most workers was that the active fraction of pollen is a protein. The authors pointed out that it was necessary to mention some of the confusing difficulties met in the past, e.g., some crude allergens possessed several chemically distinct fractions which reacted differently in different allergic persons, all of whom reacted to the unfractionated substances. Some workers ignore the fact that the complete separation of mixtures of large molecules is impossible. Biologic methods may detect traces of proteins which chemical tests would not, and certain proteins are not precipitated by reagents which usually precipitate most proteins—perchloric acid, for instance, is an excellent precipitant for most proteins but will not precipitate ovomucoid. The employment of

enzymes to destroy an ingredient in a mixture, does not remove the last traces; even chemical methods of precipitation are apt to fail in the complete removal of some organic compounds. There is no proof that all pure allergens are antigens, so caution must be used in interpreting the results of experimental sensitization. A sensitizing substance which is related in no way to the allergen may be mixed with the latter. However, these experiments are useful to demonstrate the lack of purity in the supposedly "purified" substances. The skin-reacting substance may be only a part of the allergen occurring in nature. It may resemble the hapten group, yet may not be antigenic until it is combined with a protein or polypeptide. It is possible that eventually it may be shown that there are marked differences in the chemical nature of different allergens. Even prolonged centrifugation may fail to remove very finely divided matter which is capable of producing reactions in very sensitive patients. No simple method is known for determining slight differences in the activity of two extracts of similar antigens.

STANDARDIZATION

The question of standardization of allergenic extracts has not been clarified to any great extent. It is the opinion of the reviewers that at this time the only workable method involves the use of total nitrogen determination, with additional information from biologic skin testing. Those who have had experience in the chemical determination of total nitrogen know that it is much easier than the accurate determination of protein nitrogen. The type of solution used for the precipitation of substances to be analyzed is very important, and, secondly, the method. In any event, the chemical analysis of the so-called protein nitrogen includes substances that do not fit into the strict definition of complete proteins. The evaluation of standardization by skin testing alone can also lead to much variation. The specifically sensitized skin does not always give equal or equivalent reactions even in the same individual. Suffice it to say that the skin reaction at any dilution of a solution will give only comparative reactions. This is to be expected, since the materials tested are always mixtures of antigens.

Wodehouse,[135] in a series of papers, gives much useful information on this problem. His "cutaneous reaction units" form a simple numerical system of recording reaction intensities in direct skin testing and in passive transfer experiments. Utilizing the formula $(e - w)\ w = n$, where e equals the over-all diameter of the erythema, and w the diameter of the wheal, n represents the number of cutaneous reaction units, which can be expressed by multiplying the wheal diameter by the excess of erythema diameter over that of the wheal diameter in millimeters.

Wodehouse[136] continues with this problem by using the above method of recording, using a standard pollen solution prepared by a standard method and kept under standard conditions. Potency is expressed in terms of standard nitrogen amounts per c.c. Physiologic potency is expressed as the ability to neutralize homologous reagin serum as compared to that of a standard extract. It is then, in turn, expressed in terms of the standard nitrogen units. Using the passive transfer method, as described by Prausnitz-Küstner, the neutralization is carried out *in vivo* or *in vitro,* and expressed in cutaneous reaction units.

Wodehouse,[137] in discussing the neutralization, by passive transfer method, of sera which contain reagins for both timothy and Bermuda grass, noted that one did not completely neutralize the other. This led him to the conclusion that each species of pollen possesses a predominant antigen, and one or more subordinate antigens. This also gives more evidence that the skin test alone is not the answer to standardization of allergenic extracts.

POLLEN PURITY

Ellis and Dahl[31] examined 260 different lots of dry pollen purchased from commerical sources: 68.1 per cent were found authentic and uncontaminated, 20 per cent were slightly contaminated, and in 10.4 per cent the contamination was natural in character; 6.5 per cent were incorrectly labelled, and 5.4 per cent were seriously contaminated. They suggest that certification of pollen for extraction should be required. This suggestion has been taken up by the committees on standardization of extracts of both national allergy societies, and with the help of Dr. Veldee of the U. S. Public Health Service, an attempt will be made to bring pollen, for extraction, under certain specific requirements, and be certified as to its purity.

FUNGI

Morrow[81] correlated the ten most frequently encountered fungi, reported from stations distributed throughout the U. S. They were as follows:

Alternaria	Sterile Mycelia (pale or dark)
Hormodendrum	Torula
Penicillium	Fusarium
Aspergillus	Trichoderma
Pullularia	

The first six varied in amounts at different stations. The occasional type was significant as part of the aerobiological picture of the local region, and may be responsible for a stubborn case of respiratory allergy.

Prince, Tatge and Morrow[91] reported on their further studies on mold extracts prepared by twelve modifications of their original method, using several members of the aspergillus family and alternaria. In the first five modifications in which the pellicle was treated by drying slowly or by lyophilization, and then ground before or after defatting, no significant difference was found in the skin test. Skin-reacting substances were found in the broth and washings. No histamine or histamine-like substance was found which could act as an irritant. In the next four methods, alternaria produced a very strong antigenic substance in the broth, as well as in the pellicle, whether the pellicle was washed, unwashed, defatted, dried slowly, or lyophilized.

In the next four methods, an attempt was made to separate large and small molecular aggregates, by dialysis from the broth and the unwashed pellicles. Even though the separations were not complete, definitely increased skin activity was noted from both the broth and pellicle in that part of the material which remained in the dialyzing membrane (large molecules).

Sellers and McKenzie,[110] in a study of the mold content in the air over a five-year period in the Abilene, Texas, area, showed that on exposed agar plates, molds were present throughout the entire year. In sixty-nine patients with hay fever, and in thirty-one patients with asthma and hay fever, there were sixteen instances of pure mold sensitivity, and eighty-four instances of mixed mold sensitivity. In the younger age group (one to twenty years of age), mold sensitivity particularly was prevalent.

DUST

In a comprehensive report, the standardization committee of the American College of Allergists[102] reported a co-operative investigation on the preparation and standardization of house dust extracts. Directions for the preparation and analysis of extracts known as crude concentrate, alpha picoline, and absorbed concentrate were given. Cutaneous tests showed definitely no relation to total nitrogen present, and

"some" relation to phosphotungstic-precipitated nitrogen. Successful standardization can be done by a combination of chemical and biologic methods. The chemical method involves the determination of total nitrogen and the total and free alpha amino nitrogen of the phosphotungstic acid precipitate. Such extracts are then tested biologically, and dilutions are made, based upon their chemical analysis, namely, dilution so that the extract contains .003 mg. of phosphotungstic acid precipitated nitrogen per c.c.

Rimington et al,[75,101] reporting their studies on the allergens of house dust, stated that the character of allergic substances obtained from different dusts did not differ materially. Therefore, they use a single dust supply obtained mostly from carpets. They describe their method of preparation, fractionation, concentration, and sterilization. Their material on chemical analysis contained 2 to 3 per cent nitrogen, 20 to 40 per cent hexose, and from 30 to 50 per cent ash. Hydrolysis with acid, yielded a galactose sugar, and some amino acids. Electrophoretic study at pH 8 revealed two main components, one immobile and colorless, the other mobile and colored, having similar chemical composition and equal potency when tested on dust-sensitive patients.

In a further study,[119] in which patients were tested with mold and house dust extracts in a concentration of 10^{-4}, a number found dust-sensitive also showed positive reaction to molds. Of the patients negative to dust, none gave positive reaction to molds. A striking chemical similarity was noted between the three polysaccharide products derived from molds after hydrolysis, and the dust antigen. All exhibited a polypeptide-like grouping of simple amino acids associated with a polysaccharide complex. The usual color reactions for proteins were not obtained.

Continuing their studies on dust antigen,[75] normal and allergic patients were tested in dilutions of the dust antigen 10^{-4}, 10^{-5}, and 10^{-6} concentrations. In the normal group, 58 per cent were negative to the 10^{-4} dilution, as compared with 10 per cent of the allergic group. Seventy per cent of the allergic patients showed positive reactions in a dilution of 10^{-5}. In forty-five patients who were tested with dust extract 10^{-5} dilution, cat hair, feathers, and mold extracts, thirty-five were positive to dust, and of the thirty-five, twenty-two were found sensitive to one or more of the other allergens used for testing. No patient was found who reacted to one of the other allergens but not to dust. On desensitization treatment, a definite decrease of the threshold reaction was noted, but no blocking antibody was found in the bloods of the patients so treated.

DIAGNOSIS

Healy[51] described a new type of blood test for allergen diagnosis. Using first serum and later plasma, he found that the addition of either pollen extract or histamine caused a turbidity which could be seen microscopically in many samples, and in higher dilution by means of the nephelometer in all samples. For extensive testing with a large number of allergens, high dilutions of serum or plasma were necessary to carry out such a program, and modifications were developed which formed the basis of this clinical report. The technique of the procedure was described in detail. During a period of five years, a group of 2,164 patients were studied. Of this group, a positive reaction to histamine was obtained in only 139 patients. Fifty-four other patients who were histamine-sensitive, also reacted to extrinsic factors. Eighty-nine per cent of the first group and 77 per cent of the second had relief of symptoms by treatment with histamine. Among 1,963 patients reacting to extrinsic factors, 1,732 (88 per cent) had satisfactory results.

Brown et al,[13] studying the relationship of dyspnea and diminished vital capacity as a symptom and a sign in hay fever, concluded that many patients with hay fever had a reduction in their vital capacity. In a number of these, there was no correlation between peaks and depression of their vital capacity profile as related to the dates of

pollination of the plants to which they responded with nasal symptoms. None of the patients were wheezing at the time of the determination. In the patients studied over a period of five pollen seasons, there was no apparent correlation between their diminished vital capacity and their prognosis. It was concluded from this study that among those patients in whom there was a diminished vital capacity, the majority did not materially benefit from their treatment, while the majority of those who had no diminution did benefit. Patients with hay fever should be questioned regarding dyspnea, which may be the earliest sign of bronchial involvement and additional proof of pollen sensitivity.

Schiller and Lowell [73,106] studied the effects of drugs in modifying the response to aerosolized pollen extracts, as determined by vital capacity measurements, and concluded that atropine and Pyribenzamine failed to influence pulmonary response to inhaled extracts of pollen. This is a dangerous method, since cough and severe symptoms may follow exposure to the extracts; however, the authors feel that this method is promising, particularly as the lung, the chief site of the disease process, serves as a test organ. This method also afforded an objective test, where in many cases a decrease in vital capacity may occur without the subject's being aware of any reaction.

Samter and Becker[105] reported their studies on the nasal secretions of normal and ragweed-sensitive subjects with marked skin reactivity and circulating reagins, by inserting cotton plugs saturated with 10 per cent sodium chloride solution into the nostril. Passive transfer sites were prepared with 0.1 ml. of a Seitz-filtered secretion, and retested twenty-four hours later with ragweed solution. The nasal secretions in seven of twenty ragweed patients contained ragweed reagins.

Wodehouse[139] called attention to the fact that passive transfer recipients must be carefully chosen, and it is best not to use any individual who has any allergic background. In four patients, skin-test sensitivity to ragweed developed in the course of passive transfer experiments. On requestioning, all four patients had atopic backgrounds. None developed clinical hay fever, though adequate exposure was met with in 1947. Generally, it is assumed that it is very difficult to sensitize human beings.

Stier[118] in a general discussion, evaluated allergy testing, its limitations and significance. He concluded his remarks by stating that the degree of skin reaction doesn't necessarily constitute the response of an allergen; neither does the size of the reaction indicate the severity of symptoms that can follow. The tests that gave most of the false positive and negative reactions were foods.

TREATMENT

The treatment of hay fever usually occupies the greatest amount of attention of the allergist. Therefore, any form of treatment which improves on method of administration, preparation of extracts, adjuvant materials and drugs, which either supplement or complement specific therapy, are important.

With the confusion which exists with the chemistry of pollen, the best extracts available, in the experience of the writers, are the orthodox extracts prepared by the use of aqueous solutions of the whole pollen.

Guerrant and Swineford[47] state that they can control symptoms of active hay fever by injecting dilute extracts co-seasonally. Only suspected pollens are used for skin testing, and suitable mixtures used for each case. Extracts are injected subcutaneously, starting with a dilution which gives a mild intradermal reaction, which may be as dilute as 1 to 500,000 or as strong as 1 to 10,000. Rapidly progressive amounts of extracts are injected once or twice daily, until symptoms abate or local reactions occur. When symptoms abate, tolerated amounts are injected every two or three days. Nonspecific therapy is used as an adjuvant treatment.

Mary Loveless,[70] in an attempt to apply immunologic principles to the treatment of hay fever, reported a method for the management of hay fever by the use of

Freund's adjuvant. Freund's adjuvant utilizes an emulsifying agent, mineral oil, with aqueous antigen and killed acid-fast bacilli, and a lanolin-like substance, Falba or Aquaphor. Loveless hoped to accomplish a booster effect by this method, with increased tolerance and fewer injections. She had some difficulty as she increased the dose with some reactions. However, on the whole, this method gave her thirteen excellent results, as compared to ten in a similar group of thirty patients. This method is reported as a preliminary study, and is not to be construed as a final evaluation of this type of therapy.

Lazarowitz[62] used chilling of the site of antigen injection as a method of therapy in extremely sensitive patients, in order to delay absorption. An ice bag was applied to the mid-outer part of the arm fifteen minutes before and fifteen minutes after injection. Thirty hay fever patients were treated with doses higher than those usually used, with favorable results.

Rackemann[96] discussed the bearing of pollen tolerance in the treatment of hay fever. He said that good results can be obtained with a small series of doses, provided that the amounts of these can be correlated with the tolerance of the individual. He also noted that the level of absolute tolerance appeared to be a fixed point for each patient. Generalized reactions can be minimized if the point of tolerance is recognized, and treatment kept at a lower level. Good records are essential, as the level may vary from year to year.

Koelsche,[60] of Mayo Clinic, in a general discussion of the management of hay fever, includes, besides specific desensitization, drugs for symptomatic relief, hay fever resorts, environmental control, attempts at prevention of pollination of plants, and the avoidance of constitutional reactions.

Bedford,[7] in an article discussing hay fever prophylaxis in the Royal Air Force, stated that in England most of the hay fever therapy is against timothy. He used the scratch tests with a solution containing 20,000 pollen units per c.c. The patients were injected twice a week, increasing the dose by 100 per cent until a reaction occurred. When this occurred, the dose was increased only 85 per cent until another reaction occurred. When the dose level of 50,000 pollen units per c.c. was reached, skin tests were carried out, and if the test was negative, no higher dose was given. However, if the skin test was positive, the dose was increased weekly until a negative skin test was reached. The strength of the solution used was equal to 100,000 pollen units per c.c. Side reactions were few and mild in nature. In one case, the dose level was raised to 260,000 pollen units per c.c. or 2.6 c.c. of the concentrated solution.

Zonis and Rubin[141] attempted to predict the occurrence of constitutional reaction by testing with ragweed pollen fractions. They described their method of preparation and procedure. Their results were not very encouraging, and they felt that this was due to the fact that their method of fractionization by chemical means was not sufficiently accurate to actually separate the proteins.

Rowe and Rowe,[104] discussing the occurrence of allergic symptoms in patients over the age of fifty-five, stressed the fact that seasonal allergy occurred for the first time in thirty-three of 173 patients. These patients required specific treatment, and usually responded with stronger dilutions, in the range of 1 to 500 or 1 to 50 for satisfactory results. Co-seasonal therapy required very weak dilutions in the range of 1 to 5,000,000, or 1 to 5,000,000,000. Prolonged desensitization for months, or for one or more years, was usually necessary.

Fuchs,[40] in a discussion of allergy in geriatrics, said that some patients become allergic for the first time in life at an age past fifty, and that when treated by specific methods, they respond very well.

Oral pollen therapy, using whole pollen as well as pollen propeptanes, appeared again in the literature. Egeberg and Painter[39] reported their results with oral pollen as compared to specific hyposensitization. They concluded that oral pollen therapy

offers a satisfactory method of treatment of seasonal hay fever. They felt that the advantages in this type of therapy were the absence of severe reaction and ease of administration, especially in patients who have had constitutional reactions or those who fear hypodermic medication. The treatment was more readily available for patients who must travel, or cannot come in regularly for parenteral therapy. Desensitization was more rapid. The disadvantages of oral therapy were the greater cost of material, variability of dosage, and difficulty of control, since no rigid plan of dosage was completely satisfactory.

Brown et al[14] used oral pollen therapy and studied the skin test blocking antibody response. They felt that whereas there was improvement by this method, parenterally treated patients responded much better.

Urbach et al,[125] from their studies on oral pollen propeptane therapy in hay fever, felt that the most successful alternative to subcutaneous hyposensitization with pollen extract was the oral administration of pollen. Crude pollens were likely to cause distressing gastrointestinal symptoms resulting from absorption of the undenatured antigen contained in the pollen. Urbach, in 1931, introduced oral therapy with pollen digests. These were obtained through the digestion of pollen by hydrochloric acid, pepsin, or trypsin. Urbach claimed that this procedure deprived the pollen of their native protein, but not of their type specificity. To the propeptane, the saponin glycyrrhiza was added as an adjuvant. Scientific immunologic data was advanced as added evidence for this method of treatment.

Kaplan et al,[56a] in a controlled experiment using oral whole pollen in children, concluded that oral pollen offered very little as compared to the specific hyposensitization method. When statistics were evaluated in this controlled study, the patients received little, if any, benefit from oral pollen.

Since the advent of the group of drugs classified as antihistaminics which are known to exert antiallergic properties, several studies have appeared in which these agents have been used alone or in conjunction with specific therapy. The studies of Arbesman et al,[3] Leibowitz et al,[64] and others, seem to indicate that these drugs will in no way take the place of specific hyposensitization, but merely act as symptomatic agents. In the study of Arbesman, Pyribenzamine alone relieved hay fever symptoms to about the same degree as did the specific hyposensitization therapy, plus symptomatic drugs. This study used the IBM punch cards as a means of studying variables. It is well to note that statistical studies of this type give valuable information, but actually do not give a true clinical evaluation.

A report appeared under foreign letters in the *Journal of the AMA*, from Copenhagen, on hay fever. Brunn and Schwartz[15] treated sixty-nine hay fever sufferers from 1941 to 1945 at Rigshospitals' Polyclinic Allergy Division. Sixty-three of the patients' symptoms occurred during the months of June and July. In this group, fifty-nine had good results by desensitization, which started on April 1 and continued for two months. Twenty-four to thirty injections were given in all. A number of the patients included in this group had seasonal asthma. The results of treatment were disappointing in this group.

In our experience, the patients who have pollen asthma and hay fever seem to get excellent results for the relief of asthmatic symptoms by adequate specific hyposensitization with ragweed extracts.

NONSPECIFIC HAY FEVER TREATMENT

Little of importance in the nature of nonspecific methods of therapy in hay fever has attracted our attention this year. Vitamin C has its advocates, which become smaller in number each year. Specific urinary proteose, dead for many years, is revived by an investigator who should try proteose peptone solution by injection before ascribing specificity to urinary proteose.

Edmundson[29] has been advocating a solution formally known as Metapollen, now

known as Agcuzin, which is a solution of colloidal silver, copper, and zinc. This method is a modification of the old nasal zinc ionization therapy, which was tried by many and finally dropped. His report in the *Medical Record* is enlightening. Good results were reported, except in those cases with nasal polyps, deflected septi, and broken bones obstructing the openings to the sinuses. The excellent results were accomplished by the gradual, progressive method of shrinkage. Edmundson summarized his report by stating, "There is no longer any merit in skin tests or in the determination of the offending allergen. This therapy clears up all of the classes of causation with equal completeness."

We have had no experience with this type of therapy, but on the basis of previous experience with solutions which cauterize nasal mucous membrane, we see no value over the more tried and conservative methods of therapy.

Bartlett[6] recorded his results with "Ethylene Disulphonate In Allergy," a six-year study including some 1,800 cases. Bartlett got excellent results in 412 cases of hay fever, of which 192 were adults and 220 were children. In this group, 193 were completely relieved and 135 partially relieved, with no relief in eighty-four. In 80 per cent of the hay-fever patients on this type of therapy, the results were satisfactory.

Wasson,[132] reporting on her studies with Ethylene Disulphonate over a seven-year period, still feels that it has definite merit. Among her twenty-six cases of hay fever, which were composed of sixteen adults and ten children, there was definite improvement noted in seventeen patients, and failures in nine. In summarizing her results, Wasson stated, "I don't know why Ethylene Disulphonate helps most victims of allergy, any more than I can explain the body chemistry of many other empirically successful and universally accepted pharmaceutical products."

Bodman[10] reported from Britain on his results with Ethylene Disulphonate in 160 patients, and found that of twenty-four cases with hay fever, eleven were completely relieved and four partially relieved, with no relief in nine. In this group, 62 per cent had satisfactory results. In thirty-two cases which showed definite skin tests and were treated with specific desensitization, twenty-three did not respond favorably. In seven persons who had hay fever, four had satisfactory results with Ethylene Disulphonate following specific desensitization.

It was the consensus of many men, who have had ample opportunity to study this problem of Ethylene Disulphonate, that the material has little or no value in the dilutions used, 10^{-10} to 10^{-20}. According to Avogadro's law, in a solution containing molecules dispersed by 10^{-17}, specific reacting substances would be so few that it would be possible that any given small amount would not contain any of the reacting substance.

Mertins[79] reported in the *J.A.M.A.* several cases on the excessive self-medication with Privine Hydrochloride. Severe reactions, with collapse after withdrawal of the drug, were noted. The frequency with which we meet this type of addiction, and the difficulty with which the marked withdrawal symptoms are controlled, behooves us to be wary of the uncontrolled use of this drug.

Bubert and Doenges[12] reported on the use of a new drug, Ethyl-Nor-Epinephrin (Butanefrine), which has some of the general properties of epinephrine, and which can be used to great advantage in allergy, without the severe pressor effects and central nervous system stimulation which so frequently accompanies the use of epinephrine.

The drug Allergosal (Chemtronic Laboratories), which is racemic epinephrine, has not been approved by the Council on Pharmacy and Chemistry,[18] of the A.M.A. The report stated that it was not as effective as ordinary epinephrine, and that epinephrine-fast patients did not obtain relief even by overdosage. The council felt that the unsupervised use of this potent drug was dangerous.

MISCELLANEOUS

The *Journal of the American Medical Association*,[92] in the section on queries and notes, had a number of questions asked and answered, dealing with hay fever. The question of ragweeds in Europe was answered as follows: Some members of the ragweed family are present, but in insufficient numbers to produce any appreciable amount of pollen.

The question[94] of whether or not pollen desensitization should be carried out during pregnancy was answered as follows: The slight possibility of miscarriage resulting from severe systemic reaction should not defer from its usage. Rarely, if ever, does severe hay fever bring on the above symptoms. Mothers-to-be should be kept comfortable. In our experience, hay fever desensitization, carried out at a low dose level to give some protection, is a desirable way of treating pregnant women. The precipitate[93] or sediment which is frequently found in vials of hay-fever pollen extract is probably due to some alteration in one of the chemical ingredients, which is sufficient to cause a precipitate, and is thought to belong to the polysaccharide group.

Several other notes appeared in the *J.A.M.A.*[76] which were of interest. An anti-ragweed drive was attempted in some areas in New York City. Large areas were sprayed with chemicals where the ragweed plants grew in abundance, before the pollenating stage. The Department of Sanitation and Parks, co-operating with the Health Department, destroyed over 1,000 acres of ragweed by this method.

Allergenic diagnostic and therapeutic agents have come under a change in the regulations on revision and expansion of biologics. In a publication of Federal Regulations[83] January 21, 1947, which deals with the sale of biologic products for interstate commerce, it was stated that allergenic diagnostic and therapeutic extracts may be prepared only by a licensed laboratory.

For the first time this year, a special session on allergy,[112] was held as part of the American Medical Association annual convention. Several interesting papers on hay fever and related subjects were presented.

A note appeared in the *Journal of the American Medical Association*,[82] which stated that the Marcelle Cosmetic, Inc., of Chicago, gave a grant of $1,500 to the American College of Allergists, for the standardization of pollen extracts. This work is going to be done under the direction of Morris Scherago, D.V.M., professor and head of the Department of Bacteriology, University of Kentucky.

THE ANTIHISTAMINIC DRUGS

Again this year the subject receiving the most attention in the literature was the antihistamine drugs. In reviewing this literature, we have roughly classified the reports into those dealing primarily with pharmacology and experimentations, those on clinical results, and those on side effects and reactions.

Although it is not the province of this paper to delve into the minutiae of the pharmacologic and other experimental aspects of the antihistaminics, certain reports are included to indicate the tenor of work being done in this field.

Rose, Feinberg, Friedlaender and Feinberg[103] made a careful study of comparative anaphylactic activity of Benadryl, Pyribenzamine, Antergan and Neoantergan. They studied the protective effects of the drugs against histamine by intravenous injection of histamine fifteen minutes after the animal had received the protective drug intraperitoneally. Under the conditions of the experiment, they found that Neoantergan was twenty-five times more effective in protecting the animal than Benadryl; however, the difference in antihistaminic effect was less marked as the dose of the antagonist was decreased. All of the antihistaminics protected 100 per cent of the sensitized animals against anaphylactic shock. Benadryl and Neoantergan were equally effective in inhibiting the contraction of the sensitized guinea pig intestinal strip, caused by the addition of a specific antigen. Anaphylactic contraction was in-

hibited by a lesser amount of the protective agent than that required for the histamine contraction of the same magnitude. The significance of their data was discussed in detail.

The same authors[38] compared four ethylenediamine derivatives, namely, Antergan, Pyribenzamine, Neoantergan, and Benadryl, in terms of the numbers of lethal doses of histamine, against which protection was obtained by a standard dose of 3 mg. per kg. of the drug administered intraperitoneally fifteen minutes prior to histamine injection. One hundred per cent end points of mortality were used: Benadryl protected against five, Antergan against six, Pyribenzamine against thirty-seven, and Neoantergan against 125 doses. However, preliminary studies did not show a marked difference in the antianaphylactic activity of these compounds, comparable to the above variation in histamine shock.

C. A. Winter[135] tested six compounds for antihistamine potency against intravenous histamine, histamine aerosol, and on intestinal strips against histamine *in vitro*, in guinea pigs. The descending order of potency was as follows: Neoantergan, Pyribenzamine, 3015 R.P., 3277 R.P., Benadryl and Hetramine. The ratio of the toxic dose to the effective dose was highest for Neoantergan. Side reactions, however, were least noticeable with it, and most violent after 3277 R.P.

Hamburger, Halpern, and deBray,[49] participated in research on a new series of synthetic antihistamines, which are all derived from thiodiphenylamine, and presented the results of their pharmacodynamic and clinical experiences. These drugs seemed to have greater antihistaminic properties than Antergan and Neoantergan.

In another report, Halpern[48] stated that these drugs showed marked antihistaminic and antianaphylactic activity, and are known as 3015 R.P. and 3277 R.P. The latter was able to protect guinea pigs against 1,500 lethal doses of histamine, and .1 mg. per kg. was enough to protect these animals against fatal anaphylactic shock. It might be well to mention at this point that Feinberg,[35a] commenting on this drug at a recent meeting of the Chicago Society of Allergy, stated that the amount of the drug necessary to protect against 1,500 lethal doses was so high, that if comparable dosages of some of the other antihistaminics were used, the results would approach this; that although these animals did not die immediately, surprisingly enough, twenty-four hours later, there was considerable mortality due to dissolution of the stomach and resulting peritonitis, due, no doubt, as he suggested, to the fact that there was little or no protection against the action of histamine on gastric secretion. This new chemical series is distinguished by being less toxic, and more active than earlier ones.

Mayer, Brousseau, and Eisman,[76] exposed guinea pigs to Pyribenzamine as a 2 per cent aerosol. This procedure protected them against fifteen lethal doses of histamine injected intracardially. The protection afforded by Pyribenzamine aerosol in actively sensitized guinea pigs was less regular than that in the histamine series. Passively sensitized guinea pigs were better protected than actively sensitized animals. Pyribenzamine did not produce any clinical symptoms or irritations or pathological changes in lungs exposed to this aerosol for one to two hours. It was concluded that the action of Pyribenzamine in counteracting histamine is peripheral. The drug is either selectively fixed within the receptor cells of the lungs or, by direct contact, renders the cell refractory to histamine. The therapeutic use of Pyribenzamine as an aerosol was suggested.

Pharmacodynamic studies of Pyribenzamine by Yonkman, Oppenheimer, Rennick, and Pellet,[140] by *in vitro* experiments with isolated, perfused guinea pig lung, showed that Pyribenzamine effectively antagonized histamine-induced bronchial constriction. There was a diminution of and, in over half the animals, a lack of protection in anaphylaxis. Comparable results were obtained in dogs in anaphylaxis, and it was suggested that factors other than histamine might play a role in anaphylaxis in the dog.

Campbell, Baronofsky and Good,[16] investigated the effects of Benadryl on anaphylactic and histamine shock in rabbits and guinea pigs, and found that Benadryl protected rabbits against histamine shock, but did not protect against anaphylactic shock in animals actively sensitized to egg white. These experiments seemed to indicate that a substance other than histamine is responsible for anaphylaxis.

Reporting on some experimental and clinical investigations with Antergan and Amidryl (Benadryl), Nexmand and Sylvest[84] found that when these antihistaminics were given in doses of .15 to .3 gm. orally, they could not prevent the appearance or reduce the size of histamine wheals, allergic skin reactions, Prausnitz-Küstner's reactions, and reaction produced by a stinging nettle. On the other hand, the drugs had a favorable effect in two cases of urticaria, one case of prurigo in pregnancy, and two cases of hay fever.

From Sweden, Nilzen[86] found that when Antergan and Antistine were mixed with wheal-producing substances, e.g., histamine, peptone, morphine or atropine, and injected intracutaneously, they reduced the vascular reaction considerably.

Traub, Friedmann and Landstadt[124] described a new method which enables a quantitative appraisal of antihistaminic activity from the suppression of the action of histamine on skin capillaries in the rabbit.

The regular *J.A.M.A.* Moscow correspondent[37] wrote that vitamin A was found to have a clearly determined antihistaminic effect. It is well, at this point, to note that Thienes,[123] commented on the fact that laboratory experiments with antihistamine drugs and clinical experience do not necessarily go hand in hand.

The second year of widespread use of the two most commonly known antihistaminics, Benadryl and Pyribenzamine, has, in general, not materially altered the appraisal of those investigators who reported upon them extensively last year. As Walton et al[139] said, Benadryl and probably the related antihistaminics, as at present known, will be limited in their usefulness. At best they are but symptomatic remedies. Although the immediate toxic effects are rather well known, the remote ones must be carefully considered. Allergy to these drugs is a definite possibility, and should be taken into account. In eighteen cases of seasonal hay fever, he obtained marked relief with Benadryl in sixteen cases, and slight relief in two. Toxic effects were present in fourteen cases.

McGavack, Elias and Boyd,[77] reporting on their clinical experiences with Benadryl, felt that it was an exceedingly potent antihistaminic and antispasmodic drug, which lacks unpleasant cardiovascular and nervous side effects, attendant on the use of sympathomimetic agents. Toxic reactions, while common, rarely preclude its continued use.

Logan's[68] experience of a year with Benadryl, in allergic children, indicated that it was a useful drug in the symtomatic treatment of those patients. It was used in hay fever, asthma, vasomotor rhinitis, and urticaria. In children, he stated, the effective dose depended upon the age of the child and the severity of the condition, the duration of effect, and the frequency of administration. The total daily dose varied from 1 to 12 mg. per kg. Benadryl was best administered when the stomach was empty. No marked ill effects were observed in long courses of administration. The most frequently encountered untoward reactions were drowsiness and vomiting, their incidence being approximately 24 per cent; in one case, hematuria occurred. Eleven of thirteen children with hay fever obtained some benefit. He felt that severe cases would probably respond best to a combination of Benadryl therapy and hyposensitization.

Lockey[66] believes that Benadryl is a very useful addition to our therapeutic armamentarium, especially in acute and chronic urticaria, hay fever, and perennial vasomotor rhinitis. The drug very definitely seems to have a sedative effect; it seems to counteract and neutralize the effect of epinephrine. However, careful allergic

studies and management with desensitization treatment, if indicated, are still the best procedure. Benadryl should not be used indiscriminately, as it produces serious side reactions. In thirty-two cases of hay fever with no previous treatment, six mild cases were completely relieved; in the other twenty-six, relief obtained varied from 30 to 55 per cent. The amount of relief that they obtained varied directly with the pollen count, and if it was high, the symptoms were more severe. Of forty-four cases previously treated with hyposensitization, nineteen took the drug as an adjuvant to provide symptomatic relief; most of these were relieved. It also appeared that a number of patients seemed to tolerate pollen therapy much better.

Of forty-five cases of hay fever in which Benadryl was used, Farmer and Spickschen[34] observed good results in twenty-three, fair results in eleven, and poor results in eleven. Approximately one-third of these patients experienced side effects, mainly drowsiness and dizziness. They felt that antihistaminics have a definite place in the armamentarium of allergic diseases.

One hundred and thirty-seven patients were treated with Benadryl by Blumenthal and Rosenberg,[9] who felt that the results obtained in urticaria and hay fever were encouraging. Of twenty-three patients with hay fever, fifteen were greatly relieved, five had moderate relief, and three had none. Several of their patients commented on the fact that there were occasions when they were completely relieved of symptoms, and other occasions when no relief was obtained. These authors felt that tolerance to the drug was not encountered, nor did it lose its efficacy over a long period of time. Barnett et al[5] concluded their observations on a series of patients with allergic symptoms who were on Benadryl medication, and felt that it was a valuable drug in allergy. They suggested that treatment be started with a test dose of 10 mg. per day after supper. They found that patients with low blood pressures did not tolerate large doses at first; that treatment with Benadryl is best started three weeks before the pollen season. In addition to this drug, the patient should received proper instructions in diet, elimination, rest, and hygiene. In this present report, eight more hay fever patients were added to their previous series, and all except one were adults. The dosage given these patients varied from 50 to 150 mg. per day; untoward symptoms occurred in one case, and this of no importance. They reported that all but one case was improved; however, the extent of "improvement" was not elucidated upon.

At this point it might be well to note that Reinstein and McGavack[98] reported on their technique for the administration of Benadryl. For all adult patients a schedule was prepared in which the initial dose was 150 mg. of Benadryl daily, gradually increased to 600 mg. daily over a period of ten days. The patients were told to take their medication after each meal and before retiring at night. They were instructed to stop increasing the dose as soon as symtomatic improvement began, and to remain on this effective dose for a period of two weeks; at the end of that time, medication was discontinued. If symptoms recurred, however, the patient resumed treatment. For children a similar schedule was followed, except that the maximum dose was computed on the basis of 2 mg. per pound of body weight. Unless side reactions were severe, the patient was advised to ignore them and to continue his medication as per schedule.

Pennock[89] reviewed the effectiveness of Benadryl in various allergic states. He suggested that in series in which results were poor, doses may have been inadequate. He has noted no addiction, sensitization or serious toxic effects after a year's therapy with Benadryl; there was no cumulative effect or tolerance. Of the author's patients, 57 per cent showed various side reactions; 5 per cent interrupted treatment because of these.

In the *Journal of Pediatrics,* Goldstein[45] reported his results with Benadryl on seventy-one children and eight adults. Seventy-six per cent of all groups had excellent, 10 per cent good, and 6 per cent fair to poor results; 8 per cent had no improvement. Dosage ranged from 50 to 200 mg. in the children; continuous treat-

ment was given for one week to two months. This therapy allowed the child to be in a pollen-saturated area, and yet be symptom free.

Of sixty-five patients treated with Pyribenzamine by Levin,[65] 41 per cent were improved. Best results occurred in those patients who had seasonal symptoms due to pollens. In eighteen such patients, ten (56 per cent) were improved, and eight (44 per cent) unimproved. Side reactions occurred in about 40 per cent; Levin felt, however, that they were less severe and less frequent than with Benadryl. Clinically, his feelings were that the results he obtained last year with Benadryl were slightly better than with Pyribenzamine.

Leibowitz, Kurtz, and Schwartz[64] had eighty-five patients with ragweed hay fever who received 50 mg. of Pyribenzamine twice a day. Symptomatic relief was obtained in nine of twenty-one patients with Pyribenzamine alone; in thirty-five of forty-seven patients who received Pyribenzamine and ragweed desensitization, and in ten of eighteen patients who received only specific treatment. Twenty-five of sixty-eight patients experienced side reactions such as sleepiness, palpitation, nervousness, headache, nausea, dizziness, and dryness of the mouth. The authors stressed the fact that this study was done in 1946, when the pollen count in New York City was exceptionally low.

Henderson and Rose[53] administered Pyribenzamine in an average daily dose of 200 mg. to 138 patients with various allergic complaints. The most favorable results were obtained in a group of sixty-one hay-fever victims, forty-seven of whom were benefited. Wheal reactions to scratch tests with ragweed pollen were diminished by 50 mg. of Pyribenzamine, given an hour prior to testing. Side reactions, consisting of sleepiness, nervousness, nausea, dryness of the mouth, dizziness, insomnia, headache, and vomiting, were encountered. In only two instances, was it necessary to discontinue the medication.

Fuchs, Schulman, and Strauss[41] found from their clinical studies with Pyribenzamine in hay fever that temporary symptomatic relief was afforded. However, it did not immunize or protect the hay-fever patient from the effects of the antigen-antibody reaction for any length of time. The mode of action of Pyribenzamine and similar drugs is still unknown. They feel that there is no definite proof which predicates that all allergic manifestations are the result of histamine activity. Pyribenzamine administered prior to the injection of pollen extract made possible greater dosage increases of the pollen extract, and the patients were able to reach a maximum dosage almost twice the amount they usually tolerated when taking the pollen extract alone. In the letters of the International Correspondence Society of Allergists, Green[46] stated that he similarly found that Pyribenzamine had proven to be of aid when administered prior to pollen therapy in hypersensitive patients, permitting the administration of larger amounts of antigen. He found 25 mg. to be effective, and observed no delayed local or constitutional reactions when the Pyribenzamine had been dissipated.

Feinberg and Friedlaender[36] found Pyribenzamine to be an effective palliative drug in the treatment of hay fever. Side effects were frequently encountered, but were usually mild in character. Engelsher[32] studied the effect of the antihistamine drugs, Benadryl and Pyribenzamine, on simple, multiple and mixed forms of asthma and hay fever in 193 patients he had known for a number of years. These patients were given the two drugs for a three-day trial. In 127 cases, the symptoms were either unrelieved or aggravated; the drying effect resulted in cough and asthma in some patients who never before had had chest symptoms. Of the remaining one-third, some were definitely improved, and others somewhat better. He felt that when these antihistamine drugs are compared with the standard pharmaceutic preparations used in various synergistic combinations, such as ephedrine, epinephrine, aminophylline, phenobarbital, iodides and others, the new drugs fail by far in effectiveness in allergic conditions of the respiratory tract. Although the antihistamine drugs may be

of fair to striking value in a small percentage of cases of hay fever and asthma, the vast majority of patients were not benefited.

Bernstein, Rose, and Feinberg[7a] reported that Pyribenzamine gave symptomatic relief in 82 per cent of cases with seasonal hay fever. In a smaller series, Benadryl helped 52 per cent, and Neoantergan, 65 per cent. In fifty-two patients with seasonal and nonseasonal allergic rhinitis who received both Pyribenzamine and Benadryl at different times, and in forty-four patients who received both Pyribenzamine and Neoantergan, they found that the results indicated a more favorable response to Pyribenzamine. In general, the severe hay-fever cases, or those not receiving pollen hyposensitization, did not show as much improvement as the others. The sneezing responded more favorably than the blocking; the incidence of side reactions in the entire series was 50 per cent for Benadryl, 27 per cent for Neoantergan, and 23 per cent for Pyribenzamine. They felt that these drugs are palliative remedies and are not effective in all allergic manifestations, nor in all stages of any one of them. They cannot be considered as substitutes for allergic management, such as desensitizations or elimination of allergens. It is interesting to note, that this work was done in the 1946 season which was relatively mild.

Arbesman et al[3] conducted a comparative study of Pyribenzamine versus specific hyposensitization in the treatment of pollinosis, and found that Pyribenzamine plus adequate injection therapy gave relief of symptoms in 95 per cent of 242 private patients suffering from ragweed hay fever. In clinic patients, Pyribenzamine alone relieved hay fever symptoms to about the same degree as did the specific hyposensitization therapy plus symptomatic drugs. On the other hand, injection therapy plus the usual symptomatic drugs was more superior in alleviating bronchial symptoms than was Pyribenzamine alone. Pyribenzamine alone, in sufficient dosage, may control the symptoms of seasonal allergic rhinitis to a great degree, but cannot give as adequate relief as does adequate hyposensitization treatment plus Pyribenzamine. The incidence of side effects from this drug was small when given with specific hyposensitization therapy, because smaller doses were required to control the symptoms.

A compound known as "01013," similar to Pyribenzamine, was studied by Lee et al.[63] Twenty-nine hay fever sufferers were given this drug in the fall of 1946, and, in a majority of them, symptoms were relieved. Pierce and Mothersill[88] reported on the same drug, which chemically is N, N-dimethyl-N'(2-thenyl)-N'-(2-pyridyl)-ethylene diamine. The medication exhibited its greatest effectiveness in rhinitis due to pollen sensitivity, acute urticaria, and histamine-induced headache. The effective dosage ranged from 50 to 400 mg. daily. Twenty-one ragweed hay fever cases were reported; of these, fifteen had complete relief of symptoms, three moderate relief, and three no relief. Five of these twenty-one patients exhibited side effects of headache, dizziness, depression or lightheadedness.

Again this year there were several reports published on the use of histamine azoprotein. Hebald, Cooke and Downing[52] were not able to raise the "ceiling" dosage of ragweed extract in six of eight patients with the additional treatment of histamine azoprotein. In five patients with ragweed hay fever who had never been treated before, there appeared to be no clinical benefit resulting from treatment with histamine azoprotein. Skin tests with histamine dilutions, and histamine response by subcutaneous injections, were the same before and after treatment. In no patient were precipitins specific for the histamine radicle demonstrable after histamine azoprotein injections, nor did they give protection against constitutional reactions, or protection against clinical allergy of hay fever types.

Dundy, Zohn and Chobot[24] treated twenty children and twenty adults with this preparation; of this group with various allergic complaints, ten had allergic rhinitis. They failed to find any appreciable change in the whealing response of the skin to histamine following treatment; clinically, of the group that had allergic rhinitis, two showed slight improvement. They felt that treatment with histamine azoprotein was

generally ineffective in their series. Cohen and Friedman[17] feel that a condition like hay fever, in which the exposure to the exciting allergen is maximal, cannot be prevented by treatment with histamine azoprotein. They concluded that it was of distinct value in urticaria and certain cases of bronchial asthma.

The Committee on Pharmaceuticals and Medicaments[99] of the American Academy of Allergy reported on the use of Anthallan and Pyribenzamine. Ninety-eight cases of ragweed hay fever were placed on Anthallan, and only 3 per cent benefited. In twenty-one cases of perennial allergic rhinitis, only 4 per cent received any benefit. Sixty-five per cent of those with hay fever that were given Pyribenzamine were benefited. The opinion of certain observers was that Pyribenzamine was quite capable of controlling the symptoms of hay fever without additional therapy. They note that it is important to remember, however, in the consideration of any of these figures, that the year 1946 was characterized by a relatively low pollen count, and it is highly problematic as to whether statistics obtained that year will apply at a time when the concentration of pollen in the air is very much greater. Certain side effects were noted in about 30 per cent of the cases, but in no instance were these of a serious nature. They felt that although it was not a cure for allergic diseases, it was an important adjuvant in the management of allergic diseases. Wagner[126] used Benadryl or Pyribenzamine in thirty-eight cases of hay fever, and in twenty-four (63 per cent) complete relief was obtained. Three patients derived partial relief, and eleven had none. In forty-four patients under hyposensitization treatment for hay fever but experiencing symptoms during the hay-fever season, the drugs afforded relief in thirty-eight cases. Side reactions occurred in 52 per cent of all their cases. A poor initial tolerance was frequently overcome, by decreasing the dosage for a short period of time, and then reverting to a higher dosage level.

Loveless[69-71] summarized the literature published on therapeutic and side effects of Pyribenzamine and Benadryl, and added 200 cases of her own. In comparing related data for Pyribenzamine and Benadryl, she felt that there was little difference in the efficiency of the two drugs. Side effects occurred more often after the administration of Benadryl than of Pyribenzamine; the ratio was approximately 3:1. A detailed listing of side reactions was included.

Reynolds' and Horton's[100] observations on the use of Thephorin, a new antihistamine agent, indicate that it is a useful drug in the treatment of certain types of clinical problems in which the etiological factor is probably the release of "H" substances. Since only a limited number of patients were studied, definite conclusions were not drawn. The outstanding advantages of this agent were the small dosage required for the control of symptoms, and the uniform absence of toxic manifestations. Animal studies have demonstrated the antagonism of this substance to histamine. In twenty-two cases of hay fever, seventeen had excellent results, four got 50 per cent relief, and one had no relief. It was their impression that the seventeen patients had moderately severe hay fever, while the four with 50 per cent relief had severe symptoms, and were relieved only very early in the season. One patient complained of drowsiness.

We[57] have conducted, and are still conducting, more extensive studies on this drug than these authors, and a preliminary evaluation of our results seems to corroborate these investigators' findings, namely, that small dosages are adequate, and there appears to be a uniform absence of toxic effects. However, when toxic effects are observed, they are usually of a stimulating character.

Schwartz et al[107] treated nineteen cases of hay fever with Antergan, and found that this compound was without definite effect in any case. Side effects, consisting of gastrointestinal disturbances, dizziness, et cetera, occurred frequently.

Kallos[55] felt that Antistine was a very valuable drug in the symptomatic treatment of certain allergic disorders, e.g., allergic dermatoses, serum disease, Ménière's syndrome, Horton's syndrome and certain cases of seasonal and perennial allergic

rhinitis. Antistine was of definite value for the prophylatic treatment of systemic reactions following skin testing and specific desensitization. In therapeutic doses of 100 mg. six times daily by mouth, and/or 100 mg. intravenously or intracutaneously, it did not seem to have any unfavorable side effects, although used over a long period of time (as long as eight months), and it was not habit forming.

The propensity of the antihistaminics for causing frequent side reactions, more or less mild in nature, is well known; however, it would be well to note some of the more unusual and more dangerous side effects that have been reported.

Weil[133] reported a three-and-one-half-year-old boy who was given two 50 mg. doses of Benadryl for the relief of hay fever symptoms. Six hours later a third dose of 100 mg. was administered, and twenty minutes later the child was found sitting up in bed, singing and laughing. There were muscular twitchings of the face, and involuntary spastic movements of the extremities. This was followed by urinary incontinence, and in a few minutes the child was irrational. The speech became slurred, and exaggerated patellar and triceps reflexes were noted. The child slept fitfully for several hours after administration of a sedative. On examination the next day, the child appeared normal, with no memory of the preceding night's events. Following this episode, the child tolerated Benadryl without apparent side effects.

An unusual reaction following Benadryl administration was noted by Geiger et al.[42] After 300 mg. of this drug had been taken over a period of three days, a twenty-six-year-old white woman complained of palpitation, diminished vision, malaise, drowsiness, heartburn, and nausea. Following the next regular dose of 50 mg., the patient was found unconscious. She responded to epinephrine, and three hours later had recovered completely. Seven days following the above episode, treatment with Benadryl was resumed. Once more, after 300 mg. had been taken over a period of three days, the patient complained of the same symptoms as previously mentioned; the drug was then discontinued, and the patient rapidly returned to normal.

Borman[11] noted the danger of self-medication with Benadryl, and illustrated with a case of an eighteen-year-old girl. Two 50 mg. capsules per day were prescribed for the treatment of hay fever and asthma. Excellent relief was obtained the first day, and the patient was encouraged to increase the dose herself. During the following three days, forty capsules (2,000 mg.) were ingested. She became drowsy and irrational, her temperature, pulse, respiration, and blood pressure were normal. She was treated by forced fluids, especially strong coffee, and in forty-eight hours, recovery was complete. He notes that the patient's judgment may have been affected by the first two capsules of Benadryl, thus accounting for the unusual number subsequently taken.

Schwartzberg[109] and Willerson[108] reported that Benadryl, taken in 50 mg. doses two to three times a day by a thirty-eight-year-old white man for the relief of hay fever, caused moderate drowsiness during the first week of its use. During the second week, the patient noted puffiness of the eyes and an increased number of bowel movements. In the third week a feeling of tightness in the arms, forearms, and hands developed, together with numbness and tingling of the hands, drowsiness and mental sluggishness. The drug was then discontinued, and slow improvement followed. After three months, minimal symptoms remained. Most of the above complaints appeared to be an intensification of some of the usual side effects of Benadryl. Neuritic symptoms have been produced in dogs by intravenous injections of Benadryl.

Duerfeldt[23] noted in *Northwestern Medicine* that a teen-age girl took thirty capsules of 50 mg. of Benadryl with a successful suicidal intent. Another patient, a sixty-five-year-old asthmatic, misunderstood directions and took fifty of the 50 mg. capsules at one dose and survived. He believes that all patients on this drug should be warned of its dangers. Sternberg[116] had a patient with hay fever who

was given 200 mg. of Benadryl daily for about one week, and suffered only slight side reactions. When the dosage was increased to 350 mg. a day, she developed hysteria of a severe grade. After withdrawal of the drug, she became normal within forty-eight hours. Gelfand[43] broaches the possibility of a transient hypertension, resulting from Benadryl therapy in a hay-fever patient, citing two cases in addition to his. Davidson[20] noted the fact that the taking of Benadryl interfered with skin testing.

Blanton and Owens[8] reported an interesting case of granulocytopenia, due possibly to Pyribenzamine. A seventy-four-year-old woman developed fever and marked depression of granulocytes in the peripheral blood after eight weeks of moderate doses of Pyribenzamine. Withdrawal of the drug and administration of penicillin resulted in recovery. The white cell count had dropped from 8,600 with 55 per cent neutrophiles, to 1,300 with 3 per cent neutrophiles.

Harris and Shure[50] presented a case of an eczematoid eruption, resulting from the ingestion of Pyribenzamine, and felt that this case fulfilled the criteria of an allergic reaction, because (1) it followed a suitable period of sensitization; (2) readministration after all lesions had cleared up produced an accelerated reaction (reappearance of the dermatitis within six hours); (3) the dermatitis could be reproduced at will by subsequent administration of the tablet; and (4) the reaction resulting from the ingestion of Pyribenzamine tablets was entirely independent ot the chemical and pharmacodynamic properties of Pyribenzamine.

Epstein[33] also reported the occurrence of eruptions in two patients while taking Pyribenzamine. One eruption was of the eczematoid type, the other resembled pityriasis rosea. Both cases cleared with discontinuance of the drug, and recurred on its readministration.

Kern[58] had an interesting case, a patient who had taken one tablet of Pyribenzamine after dinner, and subsequently fainted and remained unconscious for several minutes. The following morning she took another tablet after breakfast, and soon after she became very weak. A third tablet was taken after lunch; she became weak again and fainted once more. The patient was prostrated all afternoon and evening, recovered by the next day.

In the Letters of the International Correspondence Society of Allergists, Crandall[19] noted that in a period of several months he had four or five patients who had been taking large doses of either Benadryl or Pyribenzamine and had become very anemic. Their red cell count had gone down to 2.5 to 3 million, and their white cell count ranged from 1,200 to 1,500, with a preponderance of lymphocytes and a breakdown of the red cells. One patient, a physician, died from a blood dyscrasia, after being on a long course of Pyribenzamine. It is Crandall's feeling that there is a definite danger of blood dyscrasia, and that patients taking large doses over any extended period of time should be kept under close observation, taking frequent complete blood counts.

Glaser[44] confirmed the observation, made last year by Hal Davison, that in some mothers, Benadryl and Pyribenazamine greatly diminished the fetal movements. However, he had never seen any newborn infants who had any trouble attributable to the fact that the mothers had been given these drugs while pregnant.

An editorial[27] appeared in ANNALS OF ALLERGY on the antihistaminics, stating that previous comments in that organ had emphasized the fact that drugs classified as antihistaminics, such as Benadryl and Pyribenzamine, have profound hypnotic effects. The clinical results, therefore, are not unequivocal as far as their antihistaminic action is concerned. Much data indicates that the use of these drugs as antihistaminics may well be justified, where it is quite certain that histamine is the causative agent. However, in many allergic reactions, such as pollen asthma, the use of Benadryl or Pyribenzamine must be on a different basis. If it is desired to employ these drugs for their hypnotic action, we should certainly do so. We

must understand, however, that we are not using the drugs as antihistaminics, but as hypnotics.

In the *J.A.M.A.*, Waldbott[127] presented a critical inventory of the value of antihistamine drugs. He stated that in hay fever, these drugs are most beneficial in the early part of the season when the sinuses and the nasal mucosa secrete clear, watery fluid, and when there is no evidence of secondary infection. He discussed the side effects, and made mention of the possibility of the development of sensitization to these therapeutic agents. Logan[67] stated that it is well to emphasize that the use of these drugs in the control or prevention of the allergic reaction is not a substitute for thorough investigation of the allergy in question. Commenting further, he stated that if a favorable effect from these drugs is to occur, it is prompt, and rarely does one have to wait longer than an hour to observe it. The duration of the effect has varied from ninety minutes to nearly twenty-four hours. His experience in children has been that side reactions occurred in 25 to 30 per cent of the cases, and in 10 to 15 per cent were sufficiently severe to necessitate discontinuance. He doesn't feel that these drugs are designed for an indefinite period of administration. They found that many children suffering from hay fever received considerable symptomatic benefit from the use of Benadryl or Pyribenzamine. Among patients whose symptoms were severe or complicated by much asthma, the use of these two drugs was not a substitute for a program of hyposensitization with the pollen antigens responsible for the hay fever. They were useful to complement a program of hyposensitization which was giving the patient inadequate relief. He felt the dosage must be adjusted from day to day, because of the variance in pollen counts.

Wagner[126] feels that, from a clinical standpoint, the value of the antihistaminic drugs appears at present to be in the field affording temporary symptomatic relief to certain of the allergic manifestations; their significance in diagnosis and other aspects of the allergic state must await further studies. Meanwhile, they can only be considered as new drugs of certain value, but with troublesome side reactions which often limit their use. An editorialist[28] in *California Medicine* felt that the antihistaminic drugs have a field of usefulness, but that we should not allow them to throw us into the path of "drug store" medicine. The editorial further felt that though our failures for successful treatment in many patients with allergic problems were discouraging, the basic principle, to treat the cause rather than symptoms, still held.

Bret Ratner[97] arrived at the conclusion that the release of histamine has not yet proved to be the fundamental factor in anaphylaxis or allergic reactions; hence, any therapy based on such a concept must be called into question. He felt that Benadryl and Pyribenzamine and other drugs of this group have not been proved to be antihistaminic, either chemically or pharmacologically. These drugs have not proved of value in eradicating allergic syndromes. They do not appear to prevent the entrance of antigen into the circulation and the antigen-antibody reaction. It is the nature of the allergic episode to be self-limited, and it is often spontaneously terminated; for this reason, a wide variety of drugs seem to relieve it. The greatest benefits from Benadryl and Pyribenzamine are derived in acute urticaria and hay fever. These drugs must be used vigilantly, because they have serious side effects. They deserve a place as symptomatic remedies, but this author deplored the fact that some physicians and particularly the lay public felt that they were cures.

NEW BOOKS

Books dealing specifically with hay fever are lacking this year. Several books in English and in Spanish have appeared, in which the subject of hay fever was discussed.

Sterling[148] has set forth his experiences and suggestions in the treatment of hay fever. Alexander's[142] second edition of *Synopsis on Allergy* is an improved edition on the original manuscript, but is so brief that unless one has complete understanding of the subject, it is best to use a more comprehensive volume. *Office Immunology* by Sulzberger and Baer[149] contains much information, and is a valuable asset to anyone practicing allergy. Cohen's[144] English volume on allergy has been translated into Spanish, and a number of original volumes on allergy in Spanish and other foreign languages have appeared, namely, those of H. Braga,[143] Lunedei,[145] G. Ruiz Moreno,[146] R. Segre,[147] and A. Zironi.[150]

REVIEWS

The authors[56] of this present review reported in this journal a similar article covering the literature on hay fever for 1946. The only other comprehensive review of hay fever appeared in the *Archives of Otolaryngology* by MacQuiddy and King.[74] Their article is a comprehensive review of allergy, especially related to the respiratory tract.

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1947 NEW BOOKS

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144. Cohen, M. B.: Manual de alergia para el medico general.
145. Lunedei: Malattie Allergiche.
146. Ruiz Moreno, G.: Asma: Alergia.
147. Segre, R., and others: Terapeutica clinica III (2a parte) oidos, nariz y garganta alergia.
148. Sterling, A., and Hollender, B. S.: Clinical Allergy.
149. Sulzberger, M. B., and Baer, R.: Office Immunology.
150. Zirone, A.: Allergia nei tumori.

116 South Michigan Ave.
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HOTEL RESERVATION CARDS

All members planning to attend the Fall Graduate Instructional Course in Allergy to be conducted by the College under the auspices of the College of Medicine, University of Oregon, November 8-12, please write to the Secretary, 423 La Salle Medical Building, Minneapolis 2, Minnesota, for a stamped hotel reservation card. These cards will be sent to you stating the hotel rates, etc., of the headquarters hotel, the Hotel Heathman, Portland, Oregon. When filling out this card be sure to state the time of your arrival and expected departure.

News Items

AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY

The American Society of Ophthalmologic and Otolaryngologic Allergy has officially accepted membership in the International Association of Allergists.

Officers of this Society are: W. Byron Black, M.D., Kansas City, Missouri, President; Kenneth L. Craft, M.D., Indianapolis, Indiana, Vice President; and Francis L. McGannon, Lakewood, Ohio, Secretary-Treasurer. Members of the Council are: Aubrey G. Rawlins, M.D.; French K. Hansel, M.D.; Howard P. House, M.D.; William D. Gill, M.D.; William H. Evans, M.D.; Albert D. Ruedemann, M.D.; Rea E. Ashley, M.D.; and G. E. Shambaugh, M.D.

French K. Hansel, M.D., is a member of the Executive Committee of the International Association of Allergists and is one of the members of the Editorial Board of the new *International Archives of Allergy and Applied Immunology*. The S. Karger Medical Publishers of Basel, Switzerland, propose to issue the journal in the very near future.

FRENCH PHYSICIANS AWARDED FELLOWSHIPS IN ALLERGY

Two French physicians have been awarded fellowships to take a twelve-month postgraduate course in allergy which will be offered next fall by the University of Illinois' colleges of medicine and pharmacy. The physicians are Dr. Jean Dausset and Dr. Claude Lapresle, both of Paris.

They were recommended for the fellowships by Dr. Hugues Gounelle, a consultant for American Aid to France, and Dr. Andre Lichtwitz, chairman of a military-medical mission to the U. S. in 1945. At that time, Dr. Lichtwicz designated the University of Illinois as the college to train French physicians in allergy.

Eight American physicians also will be selected for the course, starting September 27. The 1948-49 course will be the fourth to be offered by the University of Illinois Allergy Unit.

NEW PROFESSIONAL TRAINING OPPORTUNITIES OFFERED ARMY DOCTORS

A revised and greatly expanded professional training program for regular Army and Reserve Medical Officers has been announced by Major General Raymond W. Bliss, Surgeon General of the Army. In line with the policy of providing in the U. S. Army the highest standard of medical care in the world, the program calls for 1900 new doctors in the Regular Army and an increasing number of volunteer Reserve officers on active duty. The program is designed to give many more Army doctors the training needed to meet the requirements for certification by the American Specialty Boards, and to further integrate civilian and military medicine. The new program will facilitate the classification and career management system already in practice in the Medical Corps whereby every effort is made to assign professional officers to posts where they can practice in their special fields of interest.

CALIFORNIA SOCIETY OF ALLERGY

An Allergy Section of the California Medical Association, known as the California Society of Allergy, held its organizational meeting at the Palace Hotel in San Francisco on April 11, 1948. Thirty allergists from the State of California were present. Dr. Willard S. Small was elected temporary chairman and Dr. Frank G. Crandall, Jr., temporary secretary.

Based upon the recommendations of the Nominating Committee, the following

officers were elected: George Piness, M.D., President; Albert H. Rowe, M.D., Vice President; Frank G. Crandall, Jr., M.D., Secretary, and Milton M. Hartman, M.D., Treasurer.

Based upon the recommendations of the Nominating Committee, the following Executive Council was elected: Giacomo R. Ancona, M.D., George Gray, M.D., George F. Harsh, M.D., Samuel H. Hurwitz, M.D., Hyman Miller, M.D., and Willard S. Small, M.D.

Dr. George Piness, chairman of the combined committee of the American Academy of Allergy and the American College of Allergists, gave a report on the progress of his committee for the establishment of an independent American Board of Allergy before the Advisory Board of Medical Specialties of the American Medical Association.

This new Allergy Section will hold its meetings in conjunction with the California Medical Association each year and will have a scientific meeting with the annual election of officers at that time. Other meetings may be called at that time if deemed necessary. All physicians in the State of California, who are interested in allergy, will be invited to attend these meetings.

The office of the Secretary, Dr. Frank G. Crandall, Jr., is Suite 210, 3875 Wilshire Blvd., Los Angeles 5, California.

CONNECTICUT ALLERGY SOCIETY

The recently organized Connecticut Allergy Society held its first meeting on Thursday, May 19, 1948, at Fairfield, Connecticut, in conjunction with the annual meeting of the Connecticut State Medical Society. During the business session a Constitution was read and adopted and the following slate of officers was elected: President—S. W. Jennes, Waterbury; Vice President—Barnett P. Freedman, New Haven; Secretary-Treasurer—Russell Webber, Waterbury; Executive Committee—A. F. Roche, Hartford, and Vincent P. Cenci, Hartford.

A round-table discussion took place on "The Anti-histaminics" which stimulated considerable exchange of views. The meeting was very well attended and gave promise for the success of the group.

Mr. and Mrs. Alfred S. Woititz, formerly of Almay, Inc., have organized the Ethix Corporation, bringing to it their wide experience in the field of hypo-allergenic cosmetics and dermatological preparations.

Ethix Corporation is initiating a series of distinguished formulas—each one supplying a specific need, all of them together forming a complete and integrated line of hypo-allergenic cosmetics and dermatological preparations.

Louis Schwartz, M.D., formerly Chief, Section of Dermatology, U. S. Public Health Service, announces the opening of his office, 915 19th Street N. W., Washington 6, D. C., Suite 713.

Jack Cohn, M.D., announces the association of Gardner S. Stout, M.D., in the practice of allergy, at 450 Sutter Street, San Francisco 8, California.

Meryl M. Fenton, M.D., announces the removal of his offices to the Marygrove Medical Center, 8830 W. McNichols Road at Kentucky, Detroit 21, Michigan.

John H. Mitchell, M.D., announces the opening of his offices at 695 Bryden Road, Columbus, Ohio.

M. Scherago, D.V.M., was elected president of the Kentucky Academy of Science in April, 1948.

BOOK REVIEWS

THE 1947 YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY. Marion B. Sulzberger, M.D., and Rudolf L. Baer, M.D. 604 pages, 13 chapters, 71 figures. Price $3.75. Chicago: The Year Book Publishers, 1947.

Many articles on the significant advances in the fields of dermatology and syphilology furnish the latest diagnostic and therapeutic procedures in cases most frequently encountered in these fields of practice. The editors endeavor to discuss and correct common misconceptions regarding dermatology held by many of the laity, nondermatologic physicians and even some dermatologists. Many of these misconceptions are due to the deplorable lack of proper facilities for teaching and research in this country as compared to the European countries.

Treatment and prevention (excluding venereal diseases) is comprehensively discussed. Details of x-ray and other physical therapy, drug eruptions (allergic and nonallergic), miscellaneous hematogenous and other dermatoses, cancers, precancerous and other tumors, mycosis fungoides, leukemia, fungus infections, infestations, venereal diseases (excluding gonorrhea), venereal diseases other than syphilis and gonorrhea, as well as investigative studies, are fully discussed. The various skin manifestations of allergy make this compact year book essential to the allergist. The paper stock, illustrations and print are of the first grade.

F. W. W.

RH FACTOR IN IMMUNOLOGICAL REACTIONS

(Continued from Page 304)

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